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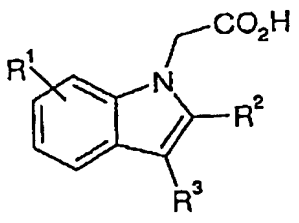
(54) Title: NOVEL SUBSTITUTED INDOLES



(I)

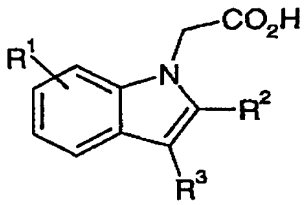
(57) Abstract: The present invention relates to substituted indoles of formula (I), useful as pharmaceutical compounds for treating respiratory disorders.

Novel substituted indoles

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTh2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has now surprisingly been found that certain indole acetic acids are active at the CRTh2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which

R^1 is hydrogen, halogen, CN, nitro, SO_2R^4, OH, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, heteroaryl, aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter five groups being optionally substituted by one or more substituents independently selected from halogen, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0,1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, CH_2OH, CH_2OR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0, 1 or 2;

R^3 is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, OH, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9CO_2H, NR^9COR^4, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{1-6} alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x = 0,1 or 2;
with the proviso that R^3 cannot be phenyl or substituted phenyl;

R^4 represents aryl, heteroaryl, or C_{1-6}alkyl all of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} and $NR^{11}R^{12}$, $S(O)_xR^{13}$ (where x = 0,1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^8 and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$, $SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x = 0,1 or 2, NR^{16}, and itself optionally substituted by C_{1-3} alkyl;

R^7 and R^{13} independently represent a C_1-C_6, alkyl, an aryl or a heteroaryl group all of which maybe optionally substituted by one or more halogen atoms;

R^8 represents a hydrogen atom, $C(O)R^9$, C_1-C_6 alkyl an aryl or a heteroaryl group, all of which may be optionally substituted by halogen atoms or an aryl group;

each of R^9 R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6 alkyl, an aryl or a heteroaryl group, all of which may be optionally substituted by a halogen atom; and

R^{16} is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, $COYC_1$-C_4alkyl where Y is O or NR^7.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear branched, or cyclic.

An example of aryl is phenyl or naphthyl.

Heteroaryl is defined as a 5-7 membered aromatic ring or can be 6,6- or 6,5-fused bicyclic each ring containing one or more heteroatoms selected from N, S and O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzisothiazole, benzisooxazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone.

Heterocyclic rings as defined for R^5 and R^6 means saturated heterocycles, examples include morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine.

Preferably R^1 is hydrogen or C_{1-6}alkyl optionally substituted by halogen, C_{1-6}alkoxy, alkylsulfone, cyano, $NR^9SO_2R^4$, NR^9COR^4. More preferably R^1 is hydrogen, methyl, methoxy, chloro, fluoro, cyano, alkylsulfone, trifluoromethyl, $NHSO_2Me$, NHCOMe. The R^1 group(s) can be present at any suitable position on the indole ring, preferably the R^1 group(s) is (are) at the 4 and/or 5-position.

When R^1 is other than hydrogen, 1 to 4 substituents can be present. Preferably the number of substituents when R^1 is other than hydrogen is 1-2.

Preferably R^2 is hydrogen, C_{1-6}alkyl or C_{1-6}alkyl optionally substituted by OR^8, more preferably R^2 is methyl.

Suitably R^3 is a 6,6- or 6,5-fused bicyclic aromatic ring optionally containing one to three heteroatoms selected from nitrogen, oxygen or sulphur, or a 5- to 7-membered heterocyclic ring containing one to three heteroatoms selected from nitrogen, oxygen or sulphur, each of the above groups being optionally substituted by one or more substituents selected from halogen, , C_{1-6}alkoxy, SO_2C_{1-6}alkyl, CN, amino, C_{1-6}alkyl, the latter group being optionally

substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0, 1 or 2,
with the proviso that R^3 cannot be phenyl or substituted phenyl.

Preferably R^3 is a 6,6-fused or 5,6-fused bicyclic aromatic ring containing at least one heteroatom, more preferably R^3 is quinoline, 1,2-benzisothiazole, benzo[b]thiophene or indole each of which is optionally substituted as defined above. More preferably R^3 is quinoline is attached to the indole at the 4 position, or 1,2-benzisothiazole and benziso[b]thiophene at the 3 positions. Most preferably R^3 is quinoline is attached to the indole at the 4-position.

Substituents can be present on any suitable position of an R^3 group. Preferred substituents include one or more selected from C_{1-6} alkyl (optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0, 1 or 2), halogen, alkoxy, alkylsulfone, cyano, substituted alkyl. More preferably the substituents are hydrogen, methyl, trifluoromethyl, methoxy, fluoro, chloro, methylsulfone, cyano.

Where R^3 is heteroaromatic, heteroatoms may be present at any suitable position of the R^3 group.

If R^3 is quinoline, preferably the substituents are present at the 2, 6,7 or (and) 8 positions. Preferably, the number of substituents other than hydrogen is 1-2.

Preferred compounds of the invention include:
3-(2-chloro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid;
2-methyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-5-methoxy-2-methyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2,6-dimethyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2,4-dimethyl-1*H*-indole-1-acetic acid;
3-(2-benzothiazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(6-fluoro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;

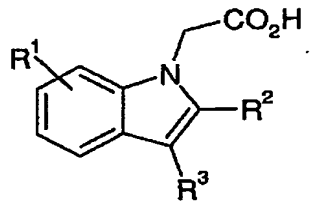
3-(1-isoquinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(6-methoxy-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(2-benzoxazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2,5-dimethyl-6-(methylsulfonyl)- 1*H*-indole-1-acetic acid;
3-(8-fluoro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(2,8-dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
2,5-dimethyl-3-[7-(trifluoromethyl)-4-quinolinyl]-1H-indole-1-acetic acid;
3-(8-bromo-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(8-methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(6,8-dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2-methyl-5-nitro-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(6-methoxy-2-methyl-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
5-methoxy-2-methyl-3-(8-methyl-4-quinolinyl)-1H-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-(8-methyl-4-quinolinyl)- 1*H*-indole-1-acetic acid;
2-methyl-3-(8-methyl-4-quinolinyl)-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2-methyl-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-chloro-2-methyl-1*H*-indol-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-4-methyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2,4-dimethyl-1*H*-indole-1-acetic acid;
3-(8-nitroquinolin-4-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid
3-(8-cyano-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(1,5-naphthyridin-4-yl)-1*H*-indole-1-acetic acid;
3-[8-(difluoromethoxy)-4-quinolinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;
5-amino-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2-methyl-5-[(methylsulfonyl)amino]-1*H*-indole-1-acetic acid;
5-(acetylamino)-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;

3-(1,2-benzisothiazol-3-yl)-7-chloro-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
3-(7-chloro-4-quinolin-4-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
5-chloro-2-methyl-3-(8-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-[3,5'-bi-1*H*-indole]-1-acetic acid;
3-benzo[*b*]thien-3-yl-5-chloro-2-methyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-thieno[2,3-*d*]pyrimidin-4-yl 1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-(hydroxymethyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-(methoxymethyl)-1*H*-indole-1-acetic acid;
2-[(acetyloxy)methyl]-5-chloro-3-(7-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylamino)methyl]-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-5,8-dihydro-4-quinolinyl)-2-(1-pyrrolidinylmethyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylthio)methyl]-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylsulfonyl)methyl]-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-4-methoxy-2-methyl-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-(2-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
2-methyl-5-(trifluoromethyl)-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(8-fluoro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)-1*H*-indole-1-acetic acid;
2-methyl-3-(8-methyl-4-quinolinyl)-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid;
2-methyl-5-(methylsulfonyl)-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
and pharmaceutically acceptable salts and solvates thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. Preferred salts include sodium salts.

In a further aspect the invention provides a compound of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

in which

R^1 is one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen, OR^7 and NR^8R^9, $S(O)_xR^7$ where x is 0,1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^7 and NR^8R^9, $S(O)_xR^7$ where x is 0,1 or 2;

R^3 is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$,

$CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{1-6} alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^7 and NR^8R^9, $S(O)_xR^7$ where x = 0,1 or 2;
with the proviso that R^3 cannot be phenyl;

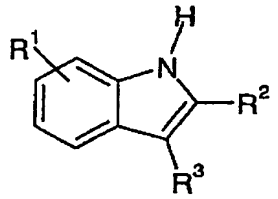
R^4 represents hydrogen or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} and $NR^{11}R^{12}$ $S(O)_xR^{13}$ (where x = 0,1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^{13} and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x = 0,1 or 2, NR^{16}, and itself optionally substituted by C_{1-3} alkyl;

each of R^7, R^8, R^9 R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6, alkyl, an aryl or a heteroaryl group; and

R^{16} is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, $COYC_1$-C_4alkyl, Y is O or NR^7.

In a further aspect the invention provides a process for the preparation of a compound of formula (I)/(IA) which comprises reaction of a compound of formula (II):



(II)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

$L\text{-}CH_2CO_2R^{17}$ (III)

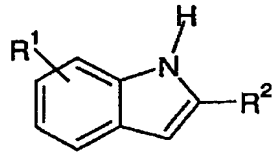
where R^{17} is an alkyl group and L is a leaving group in the presence of a base, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R^{17} to the corresponding acid
- forming a pharmaceutically acceptable salt.

The reaction can be carried out in a suitable solvent such as THF using a base such as sodium hydride, caesium carbonate or the like. Suitable groups R^{17} include C_{1-6} alkyl groups such as methyl, ethyl or *tertiary* butyl. Suitable L is a leaving group such as halo, in particular bromo or chloro. Preferably the compound of formula (III) is ethyl bromoacetate.

Hydrolysis of the ester group R^{17} can be carried out using routine procedures, for example by stirring with aqueous sodium hydroxide.

Compounds of formula (II) can be prepared by reacting a compound of formula (IV):



(IV)

in which R^1 and R^2 are as defined in formula (I) or are protected derivatives thereof, with a base and a compound of formula (V):

$R^3\text{-}L^2$ (V)

in which R^3 is as defined in formula (I) or is a protected derivative thereof, and L^2 is a leaving group, and optionally thereafter removing any protecting groups.

Suitable bases are those which will de-protonate the indole, including Grignard reagents such as ethylmagnesium bromide. The reaction is carried out in an inert nitrogen atmosphere in a solvent such as THF. Suitable L^2 is halogen, for example chloro.

Or compounds of formula (II) can be prepared by heating a compound of formula (IV) with a compound of formula (V). The reaction can be carried out in an inert atmosphere in a solvent such as DMF or NMP and optionally thereafter removing any protecting groups.

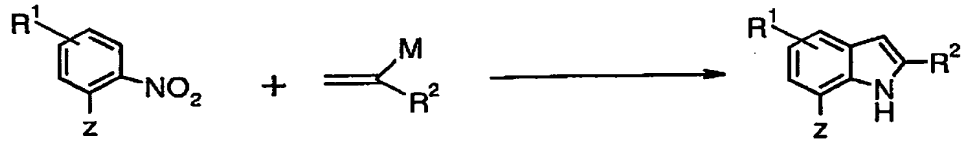
Compounds of formula (II) can be prepared from compounds of formula (VI).

(VI) (II)

In which Z is a halogen atom, preferably chlorine or bromine in which R^1 and R^2 or protected derivatives thereof are as defined in formula (I).

The reaction is carried out under a hydrogen atmosphere in the presence of a catalyst, preferably palladium on charcoal in a solvent, such as ethanol.

Compounds of formula (VI) can be prepared by reaction with compounds of formula (VII) with compounds of formula (VIII).



(VII) (VIII) (VI)

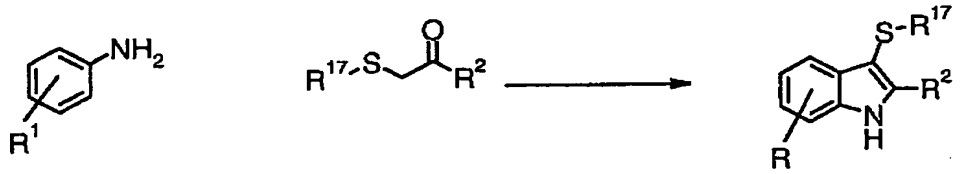
The reaction is carried out at -40°C in a suitable solvent such as THF. M is a metal halide such as magnesium bromide, R^1 and R^2 are as described in formula (I) or protected derivatives thereof. Some compounds of formulae (IV), (V), (VII) and (VIII) are commercially available or can be prepared using standard chemistry well known in the art.

Alternatively compounds of formula (IV) can be prepared by reacting a compound of formula (IX) with a thiol in acidic conditions, such as thiosalycilic acid and trifluoroacetic acid

(IX) (IV)

Where R^1 and R^2 are as described in formula (I) or protected derivatives thereof and R^{18} is alkyl or substituted aryl, preferably R^{18} is 4-chlorophenyl or methyl.

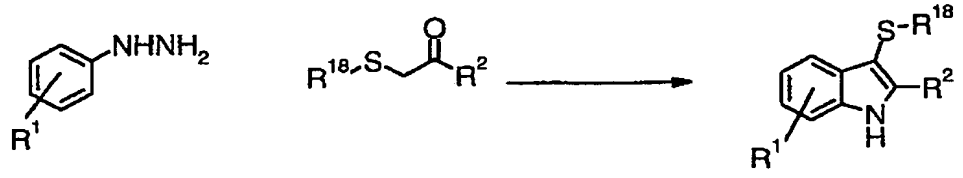
Compounds of formula (IX) can be prepared by reacting a compound of formula (X) with a compound of formula (XI).



(X) (XI) (IX)

The reaction can be carried out in the presence of a chlorinating agent. Preferably the reaction is carried out using sulfonyl chloride or *tert*-butyl hypochlorite in a solvent such as dichloromethane or THF.[1]

Or, compounds of formula (IX) can be prepared by reacting a compound of formula (XI) with a compound of formula (VII).

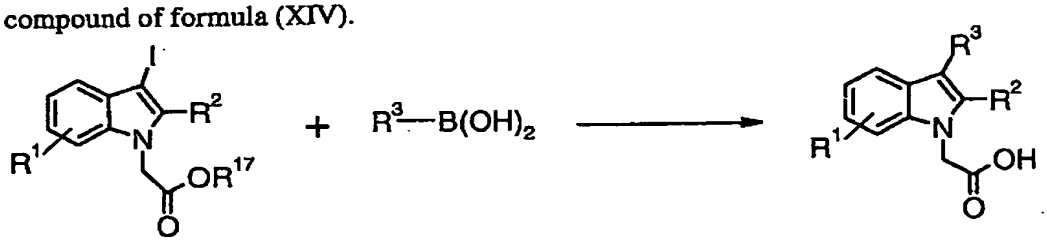


(XII) (XI) (IX)

The reaction is carried out in a suitable solvent such as acetonitrile.

Compounds of formulae (X), (XI) and (XII) are commercially available or can be prepared using methods well known in the art, in which R^1 and R^2 or protected derivatives thereof are as defined in formula (I).

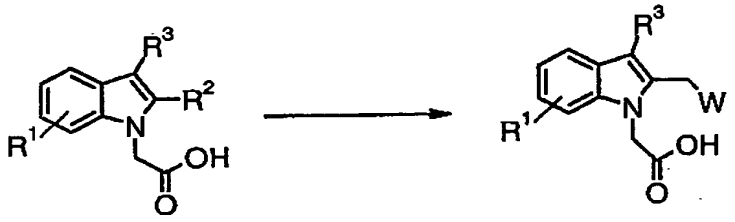
Compounds of formula (I) can also be prepared from compounds of formula (XIII) with a compound of formula (XIV).



(XIII) (XIV) (I)

The reaction is carried out using a palladium catalyst with a suitable ligand, such as tri(*o*-tolyl) phosphine in an organic solvent. A compound of formula (I) is obtained directly as described or the corresponding ester is obtained, which can be hydrolysed as outlined above.

Or, certain compounds of formula (I) can be prepared by reaction of compounds of formula (XV) with a suitable nucleophile, for example alkoxy or amino.



(I) (XV)

in which R^1 and R^2 or protected derivatives thereof are as defined in formula (I). W is a a halogen atom, preferably bromine or chlorine.

Compounds of formula (XV) are prepared from compounds of formula (I) where R^2 is methyl.

(I) (XV)

Certain compounds of formulae (IV), (VI), (VII), (VIII), (IX), (XIII) and (XV) or protected derivatives thereof are believed to be novel and form a further aspect of the invention.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

In a further aspect, the present invention provides the use of a compound of formula (I), pharmaceutically acceptable salt or solvate thereof for use in therapy.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)); chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofoulous rhinitis, **perennial allergic rhinitis,** easonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

(2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areatacorneal ulcer and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal diorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs hepatitis

(alcoholic, steatohepatitis and chronic viral) , glomerulonephritis, renal impairment, chronic renal failure and other organs

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) the title and sub-titled compounds of the examples and methods were named using the ACD labs/name program (version 6.0) from Advanced Chemical Development Inc, Canada;

(ii) unless stated otherwise, reverse phase preparative HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(iii) Flash column chromatography refers to normal phase silica chromatography

(iv) solvents were dried with $MgSO_4$ or Na_2SO_4;

(v) Evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(vi) Unless otherwise stated, operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(vii) yields are given for illustration only and are not necessarily the maximum attainable;

(viii) the structures of the end-products of the formula (1) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(ix) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), infra-red (IR) or NMR analysis;

(x) mass spectra (MS): generally only ions which indicate the parent mass are reported when given, ^1H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal

standard;

(xi) the following abbreviations are used:

EtOAc	Ethylacetate
DMF	*N,N*-Dimethyl formamide
NMP	N-methylpyrrolidine
THF	tetrahydrofuran
RT	room temperature
TFA	trifluoroacetic acid
H	hour

Example 1

3-(2-chloro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 7-chloro-4-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

2,5-dimethylindole (500 mg) was dissolved in dry toluene (2 ml), and maintained under a nitrogen atmosphere. The reaction was cooled to 0 °C before adding EtMgBr (2.5 ml, 3M in Et_2O) dropwise, keeping the temperature below 5 °C. Allowed the mixture to warm to RT and stirred for 0.5 h. A solution of 4, 7-dichloroquinoline (680 mg) in dry THF (3 ml) was added slowly to the reaction. After stirring for 30 minutes at RT the reaction was slowly heated to 90 °C and stirred overnight. The reaction was allowed to cool to RT before adding EtOAc and water to the mixture. The organic layer was separated and the organic layer was extracted with EtOAc (x 3). The combined organics were washed with saturated aqueous NH_4Cl, H_2O and brine then dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Purification by chromatography eluting with 15% acetone/isohexane gave the sub-title compound (0.47 g).

MS: ESI (+ve): 307 (M+1, 100%)

b) 3-(2-chloro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid

7-chloro-4-(2,5-dimethyl-1*H*-indol-3-yl)quinoline (370 mg) was dissolved in dry THF (8ml), and maintained under a nitrogen atmosphere. The reaction was cooled to –5 °C before slowly adding NaH (53 mg, 60% dispersion in mineral oil) portion-wise. Allowed the mixture to warm to RT and stirred for 40 minutes. The mixture was cooled to 0 °C before adding ethyl bromoacetate (0.147 ml) dropwise. After stirring for 1 hour at 15 °C, the reaction was diluted with EtOH (5 ml) and 10% aqueous NaOH solution (3 ml). Stirring over night at RT converted the ethyl ester to the acid. Acidified with 1M aqueous HCl and extracted with EtOAc (x 3). The combined organics were washed with water and brine then dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Further purification was by solid phase extraction using NH_2 sorbent (6.5 g), eluting CH_3CN and 20% AcOH/CH_3CN. The solvent was evaporated under reduced pressure and the residue was azeotroped using toluene. This gave the title compound (378 mg).

MS: ESI (+ve): 366 (M+1)

^{1}H NMR (DMSO-d6) δ 8.97(1H, d), 8.14 (1H, d), 7.77 (1H, d), 7.56 (1H, dd), 7.49 (1H, d), 7.33 (1H, d), 6.99 - 6.92 (2H, m), 4.47 (2H, m), 2.29 (3H, s),2.21 (3H, s).

Example 2

3-(2-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.
MS: ESI (+ve): 351 (M+1).
^{1}H NMR (DMSO-d6) δ 9.14 (1H, d), 8.30 (1H, d),. 7.89 (1H, d), 7.79 - 7.72 (2H, m), 7.59 (1H, d), 7.27 - 7.19 (2H, m), 7.12 - 7.06 (1H, m), 5.18 (2H, s), 2.32 (3H, s).

Example 3

3-(2-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.
MS: ESI (+ve): 337 (M+1).
^{1}H NMR (DMSO) δ 8.21 (1H, d), 8.14 (1H, m), 7.86 (1H, s), 7.61-7.66 (2H, m), 7.56 (2H, d), 7.24 - 7.30 (m, 1H), 7.12 - 7.19 (1H, m) and 5.12 (3H, s).

Example 4

2-methyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.
MS: ESI (+ve): 317 (M+1).
^{1}H NMR DMSO δ 8.97 (1H, d), 8.11 (1H, d), 7.70 - 7.82 (2H, m), 7.45 -7.57 (3H, m), 7.09 -7.22 (2H, m), 6.99 - 7.07 (1H, m), 5.13 (2H, s), 2.26 (3H, s).

Example 5

3-(2-chloro-4-quinolinyl)-5-methoxy-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.
MS: APCI (M+H): 381
^{1}H NMR (DMSO-d6) δ 8.99 (1H, d), 8.16 (1H, d), 7.76(1H, d), 7.63-7.56 (m, 1H), 7.52 (1H, d), 7.45 (1H, d), 6.81 (1H, dd), 6.61 (1H, d), 5.07 (2H, s), 3.62(3H, s) and 2.22(3H, s).

Example 6

3-(2-chloro-4-quinolinyl)-2,6-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.
MS: APCI (M+H): 365
^{1}H NMR (DMSO-d6) δ 8.99 (1H, d), 8.18 (1H, d), 7.77(1H, d), 7.59 (1H, dd), 7.50 (1H, d), 7.36 (1H, d), 7.02 (1H, d), 6.85 (1H, d), 5.06 (2H, s), 2.42 (3H, s) and 2.24 (3H, s).

Example 7

3-(2-chloro-4-quinolinyl)-2,4-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1.

MS: APCI $[M+H]^+$: 365

^{1}H NMR (DMSO-d6) δ 8.97 (1H, d), 8.13 (1H, d), 7.50-7.61 (2H, m), 7.47 (1H, d), 7.24 (1H, d), 6.95 - 7.02 (1H, m), 6.70 (1H, d), 4.63 (2H, s), 2.05 (3H, s) and 1.74 (3H, d).

Example 8

3-(2-benzothiazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared in an analogous method as for preparation of Example 1 using 2-chloro-1,3-benzothiazole.

MS: ESI (-ve) 321 (M-1)

Example 9

2,5-dimethyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

a) 4-(2,5-dimethyl-1*H*-indol-3-yl)-7-methyl-quinoline

The sub-title compound was prepared by the method of Example 1 step a) using 2,5-dimethyl indole and 4-chloro-7-methyl-quinoline.

^{1}H NMR DMSO δ 11.34(1H,s), 7.99(1H,dd), 7.70(2H,ddd), 7.46-7.4(1H,m), 7.35(1H,s), 7.28(1H,s), 6.92(1H,dd), 6.89(1H,s), 2.72(3H,s), 2.27(3H, s).

b) 2,5-dimethyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid, ethyl ester

The title compound was prepared by the method of Example 1 step b) using the product of step a).

MS: ESI (+ve) 344 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 7.99(1H,dd), 7.72-7.68(1H,m), 7.66(1H,d), 7.43(1H,dd), 7.38(1H,d), 6.97(1H,d), 6.92(1H,s), 5.00(2H,s), 2.71(3H,s), 2.29(3H, s) and 2.21(3H,s).

Example 10

2,5-dimethyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid, sodium salt

a) 8-Methyl-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

2,5-Dimethylindole (290 mg) and 8-methyl-4-chloroquinoline (360 mg) were suspended in *N*-methylpyrolidinone (0.5 ml), and maintained under a nitrogen atmosphere. The reaction was heated to 140°°C with stirring for 45 minutes. On cooling a deep red precipitate formed, the mixture was diluted with diethylether and the solid collected by filtration,and dried to give the sub-title compound (570 mg).

MS: ESI (+ve): 287 $[M+H]^+$

b) Ethyl [3-(8-Methyl-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetate

8-Methyl-4-(2,5-dimethyl-1*H*-indol-3-yl)quinoline (0.57 g) and caesium carbonate (1.28 g) were suspended in dry acetone (100 ml), followed by addition of ethyl bromoacetate (0.37g) and maintained under a nitrogen atmosphere. The reaction was heated to reflux for 24 h. Further quantities of caesium carbonate (0.64 g) and ethyl bromoacetate (0.19g) were required to complete the reaction after a further 6 hours. The solvents were evaporated under reduced pressure and the residue purified by silica flash chromatography using 8:1 isohexane/acetone as eluent to give the sub-title compound (35 mg).
MS: ESI (+ve): 373 $[M+H]^+$

c) 2,5-Dimethyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid, monosodium salt
The product obtained from Step b (0.30 g) was suspended in methanol (20 ml) and to it added 1.0M sodium hydroxide (0.81 ml) for the mixture to be stirred overnight at room temperature to complete the reaction. The solution was evaporated to dryness and triturated with diethyl ether to give an off-white solid which was collected by filtration and dried under vacuum at 40°C overnight (0.30 g) to give the title compound.
MS: ESI (+ve): 345 $[M+H]^+$
^{1}H NMR (DMSO-d6) δ 8.95 (1H, d), 7.62 (2H, t), 7.46 - 7.34 (2H, m), 7.24 (1H, d), 6.93 - 6.88 (2H, m), 4.46 (2H, d), 2.79 (3H, s), 2.28 (3H, s), 2.20 (3H, s)

Example 11
3-(6-fluoro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, sodium salt
a) 6-Fluoro-4-(2,5-dimethyl-1*H*-indol-3-yl)quinoline
The sub-title compound was prepared by the method of Example 10 part a, using 2,5-dimethyl indole and 4-chloro-6-fluoroquinoline.
MS: ESI (+ve): 291 $[M+H]^+$

b) Ethyl [3-(6-Fluoroquinolin-4-yl)-2,5-dimethyl-1*H*-indol-1-yl]acetate
The sub-title compound was prepared by the method of Example 10 part b, using the product of part a.
MS: ESI (+ve): 377 $[M+H]^+$

c) 3-(6-Fluoro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, sodium salt
The title compound was prepared by the method of Example 10 part c, using the product of part b.
MS: ESI (+ve): 349 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 8.93 (1H, d), 8.16 (1H, dd), 7.69 (1H, td), 7.48 (1H, d), 7.41 (1H, dd), 7.26 (1H, d), 6.96 - 6.91 (2H, m), 4.45 (2H, s), , 2.30 (3H, s), 2.21 (3H, s)

Example 12

3-(1-isoquinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, sodium salt

a) 1-(2,5-Dimethylindol-3-yl)isoquinoline.

The sub-title compound was prepared by the method of Example 10 part a, using 2,5-dimethyl indole and 1-chloroisoquinoline.

MS: ESI (+ve): 273 $[M+H]^+$

b) Ethyl [2,5-dimethyl-3-(isoquinolin-1-yl)-1*H*-indol-1-yl]acetate.

The sub-title compound was prepared by the method of Example 10 part b, using the product of part a.

MS: ESI (+ve): 359 $[M+H]^+$

c) 3-(1-isoquinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, monosodium salt

The title compound was prepared by the method of Example 10 part c, using the product of part b.

MS: ESI (+ve): 331 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 8.60 (1H, d), 8.01 (1H, d), 7.91 (1H, d), 7.75 (2H, dd), 7.55 (1H, dd), 7.23 (1H, d), 6.95 (1H, s), 6.89 (2H, dd), 4.46 (2H, q), 2.27 (3H, s), 2.24 (3H, s).

Example 13

3-(6-Methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, sodium salt

a) 6-Methoxy-2-methyl-4-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

The sub-title compound was prepared by the method of Example 10 part a, using 2,5-dimethyl indole and 4-chloro-6-methoxy-2-methylquinoline.

MS: ESI (+ve): 317 $[M+H]^+$

b) Ethyl [3-(6-methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1]acetate

The sub-title compound was prepared by the method of Example 10 part b, using the product of part a.

MS: ESI (+ve): 403 $[M+H]^+$

c) 3-(6-methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, monosodium salt

The title compound was prepared by the method of Example 10 part c, using the product of part b.

MS: ESI (+ve): 375 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 7.89 (1H, d), 7.35 (1H, dd), 7.29 (1H, s), 7.25 (1H, d), 7.11 (1H, d), 6.99 (1H, s), 6.91 (1H, dd), 4.45 (2H, q), 3.65 (3H, s), 2.65 (3H, d), 2.32 (3H, d), 2.22 (3H, s)

Example 14

2,5-dimethyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid, sodium salt

The product from Example 10, step c) (24 mg) was suspended in ethanol (50 ml) and triethylamine (1 ml) and hydrogenated at 1.5 bar in the presence of 10% palladium on charcoal (24 mg) overnight. The mixture was filtered through celite and the filtrate evaporated and the resultant precipitate triturated with diethyl ether to give the title compound as a yellow powder (90 mg).

MS: ESI (+ve): 331 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 8.94 (1H, d), 8.09 (1H, d), 7.76 (2H, m), 7.52 (1H, t), 7.45 (1H, d), 7.33 (1H, d), 6.94 (2H, d), 4.77 (2H, s), 2.26 (3H, d), 2.23 (3H, d)

Example 15

2,5-Dimethyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-8-(trifluoromethyl)-quinoline, hydrochloride

A mixture of 2,5-dimethylindole (765 mg) and 4-chloro-8-trifluoromethylquinoline (1.22 g) in NMP (1.5 ml) and 4M HCl in dioxane (0.2 ml) was heated at 140 °C for 1 h. After cooling the mixture was triturated with ether and filtered to give the sub-title compound (1.33 g) as a dark red solid.

MS: ESI (+ve): 341 $[M+H]^+$ 100%

Alternative Method

A solution of 2,5-dimethylindole (675 mg) in dioxane (1.5 ml) was added to a solution of 4-chloro-8-trifluoromethylquinoline (1.08 g) in 2M HCl in dioxane (2.2 ml) at 80 °C and the resultant solution was heated at 100 °C for 1h. After cooling the mixture was diluted with ether and the precipitate was collected to give the sub-title compound (1.44 g), identical to that prepared above.

b) Ethyl 2,5-dimethyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetate

A mixture of the product from step a) (1.74 g), ethyl bromoacetate (0.62 ml) and caesium carbonate (3.15 g) in dry acetone (45 ml) was heated under reflux under nitrogen for 32 hours. Water and aq. ammonium chloride solution were added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, petrol-acetone as eluent) to give the sub-title compound (1.63 g).

MS: ESI (+ve): 427 $[M+H]^+$ 100%

c) 2,5-Dimethyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

A solution of product from step b) (1.46 g) and 1 M sodium hydroxide (3.42 ml) in THF (20 ml) and methanol (2 ml) was stirred for 16 hours. The solvent was removed *in vacuo* and the residue was dissolved in water (20 ml) and washed with dichloromethane. 1M HCl (3.4 ml) was added slowly to the stirred solution. The precipitate was collected and dried to give the title compound (1.23 g. M.p. 145 °C.

MS: ESI (+ve): 399 $[M+H]^+$ 100%

^1H NMR (DMSO-d6) δ 2.24 (3H, s), 9.11 (1H, d), 8.21 (1H, d), 8.02 (1H, d), 7.67 (1H, t) 7.63 (1H, d), 7.44 (1H, d), 7.01 (1H, d), 6.95 (1H, s), 5.12 (2H, s), 2.31 (3H, d).

Example 16

3-(2-benzoxazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 2-(2,5-dimethyl-1*H*-indol-3-yl)-benzoxazole

2,5-dimethyl indole (0.3g), 2-chlorooxazole(0.47g) and NMP (2ml) were heated in a microwave at 100watts for 20 min at 160°C. Water ane EtOAc were added and separated, the aqueous phase was re-extracted with EtOAc (x 4). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The precipitate was triturated with EtOAc then recrystallised from methanol to give the title compound (0.19g).

MS: ESI (+ve): 263 $[M+H]^+$

Where is reaction b)?

c) 3-(2-benzoxazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 1 part b, using the product of step a).

^1H NMR (DMSO-d6) δ 8.15 (1H ,s), 7.78-7.63 (2H, m), 7.39-7.22 (3H ,m), 7.0 (1H, d), 4.5 (2H,s), 2.83 (3H, s) and 2.81 (3H, s).

Example 17

3-(1,2-Benzisothiazol-3-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid, sodium salt

a) 3-(2,5-dimethyl-1*H*-indol-3-yl)-1,2-benzisothiazole

The sub-title compound was prepared by the method of Example 10 part a, using 2,5-dimethyl indole and 3-chloro-1,2-benzisothiazole.

MS: ESI (+ve): 279 $[M+H]^+$

b) Ethyl 3-(1,2-benzisothiazol-3-yl)-2,5-dimethyl-1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 10 part b.

MS: ESI (+ve): 365 $[M+H]^+$

c) 3-(1,2-benzisothiazol-3-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid

The sub-title compound was prepared by the method of Example 10 part c, using the product of step b).

^{1}H NMR (DMSO-d6) δ 8.3(1H, d), 7.8(1H,d), 7.6(1H,d), 7.5(1H,t), 7.3(1H,d), 7.25(1H, s), 6.95(1H,d), 2.4(3H,s), 2.32(3H,s).

Examle 18

3-(7-chloro-4-quinolinyl)-2,5-dimethyl-6-(methylsulfonyl)- 1*H*-indole-1-acetic acid

a) 7-chloro-4-[2,5-dimethyl-6-(methylsulfonyl)-1*H*-indol-3-yl]-quinoline

Trifluoroacetic anhydride (few drops) and methane sulfonic anhydride (0.114 ml x3) were added to the product of Example 1 part a) in a sealed tube, and heated to 100 °C for 6 hours and then 24 hours. The residue was passed through silica eluting with MeOH/dichloromethane (9:1v/v). This was further purified by RPHPLC eluting with acetonitrile/ammonium acetate (25/75 to 95/05) to give the sub-title compound (66 mg).

MS: ESI (-ve): 383 $[M-H]^-$

b) 3-(7-chloro-4-quinolinyl)-2,5-dimethyl-6-(methylsulfonyl)-1*H*-indole-1-acetic acid

The title compound was prepared by the method of ExampleExample 1 part b) using the product of step a).

^{1}H NMR (DMSO-d6) δ 9.01(1H,d), 8.17(1H,d), 7.96(1H,d), 7.72(1H,d), 7.56-7.6(1H,m), 7.51(1H,d), 7.14(1H,s), 4.55(2H,d), 3.20(3H,s), 2.60(3H,s) and 2.27(3H,s).

Example 19

3-(8-Fluoro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-8-fluoroquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a, using 2,5-dimethylindole and 4-chloro-8-fluoroquinoline.

MS: ESI (+ve): 291 $[M-Cl]^+$

b) Ethyl 3-(8-fluoro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b, using the product of step a).

MS: ESI (+ve): 377 $[M+H]^+$

c) 3-(8-Fluoro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid

The title compound was prepared by the method of Example 10 step c, using the product of step b).

MS: ESI (+ve): 349 $[M-Na+2H]^+$

^1H NMR (DMSO-d6) δ 8.98 (1H, d), 7.63 (1H, d), 7.56 (1H, d), 7.46 (2H, d), 7.40 (1H, m), 6.98 (1H, d), 6.91 (1H, s), 4.45 (2H, t), 2.31 (3H, s), 2.23 (3H, s)

Example 20

3-(2,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-2,8-dimethylquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a, using 2,5-dimethylindole and 4-chloro-2,8-dimethylquinoline.

(MS: ESI (+ve): 301 $[M-Cl]^+$

b) Ethyl 3-(2,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b, using the product of step a).

MS: ESI (+ve): 387 $[M+H]^+$, 100%.

c) 3-(2,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c, using the product of step b).

MS: ESI (+ve): 359 $[M-Na+2H]^+$

^{1}H NMR (DMSO-d6) δ 6.94 (1H, d), 6.81 (1H, d), 6.63 (1H, s), 6.54 (2H, m), 6.24 (1H, d), 6.21 (1H, d), 3.92 (2H, dd), 2.08 (3H, s), 2.05 (3H, s), 1.60 (3H, s), 1.54 (3H, s)

Example 21

2,5-Dimethyl-3-[7-(trifluoromethyl)-4-quinolinyl]-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-7-(trifluoromethyl)-quinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a, using 2,5-dimethylindole and 4-chloro-7-trifluoromethylquinoline.

MS: ESI (+ve): 341 $[M-Cl]^+$

b) Ethyl 2,5-dimethyl-3-[7-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b, using the product of step a).

MS: ESI (+ve): 427 $[M+H]^+$

c) 2,5-Dimethyl-3-[7-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c, using the product of step b).

MS: ESI (+ve): 399 $[M-Na+2H]^+$

^{1}H NMR (DMSO-d6) δ 9.09 (1H, d), 8.43 (1H, s), 8.02 (1H, d), 7.79 (1H, dd), 7.61 (1H, d), 7.27 (1H, d), 6.95 (1H, s), 6.94 (1H, d), 4.44 (2H, t), 2.31 (3H, s), 2.25 (3H, s)

Example 22

3-(8-Bromo-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 8-Bromo-4-(2,5-dimethyl-1*H*-indol-3-yl)-2-methylquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a, using 2,5-dimethylindole and 8-bromo-4-chloro-2-methylquinoline.

MS: ESI (+ve): 365/7 $[M-Cl]^+$, 100%.

b) Ethyl 3-(8-Bromo-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b, using the product of step a).

MS: ESI (+ve): 451/3 $[M+H]^+$, 100%.

c) 3-(8-Bromo-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c, using the product of step b).

MS: ESI (+ve): 423/5 $[M-Na+2H]^+$, 100%.

^1H NMR (DMSO-d6) δ 8.08 (1H, d), 7.74 (1H, d), 7.41 (1H, s), 7.33 (1H, t), 7.25 (1H, d), 6.93-6.89 (2H, m), 4.45 (2H, dd), 2.77 (3H, s), 2.31 (3H, s), 2.23 (3H, s)

Example 23

3-(8-Methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-8-methoxy-2-methylquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a), using 2,5-dimethylindole and 4-chloro-8-methoxy-2-methylquinoline.

MS: ESI (+ve): 303 $[M-Cl]^+$, 100%.

b) Ethyl 3-(8-methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b), using the product of step a).

MS: ESI (+ve): 389 $[M+H]^+$, 100%.

c) 3-(8-Methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c), using the product of step b).

MS: ESI (+ve): 361 $[M-Na+2H]^+$, 100%

^1H NMR (DMSO-d6) δ 8.86 (1H, d), 7.46 (1H, m), 7.39 (1H, d), 7.33 (1H, dd), 7.24 (1H, d), 7.19 (1H, d), 6.92-6.88 (2H, m), 4.44 (2H, dd), 4.02 (3H, s), 2.30 (3H, s), 2.21 (3H, s)

Example 24

3-(6,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-6,8-dimethylquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a) using 2,5-dimethylindole and 4-chloro-6,8-dimethylquinoline.

MS: ESI (+ve): 301 $[M-Cl]^+$

b) Ethyl 3-(6,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b), using the product of step a).

MS: ESI (+ve): 387 $[M+H]^+$

c) 3-(6,8-Dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c) using the product of step b).

MS: ESI (+ve): 359 $[M-Na+2H]^+$

^{1}H NMR (DMSO-d6) δ 8.86 (1H, d), 7.44 (2H, d), 7.37 (1H, d), 7.23 (1H, d), 6.92-6.88 (2H, m), 4.45 (2H, s), 2.77 (3H, s), 2.36 (3H, s), 2.30 (3H, s), 2.21 (3H, s)

Example 25

3-(8-Chloro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-8-chloroquinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a), using 2,5-dimethylindole and 4,8-dichloroquinoline.

MS: ESI (+ve): 307 $[M-Cl]^+$

b) Ethyl 3-(8-chloro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b), using the product of step a).

MS: ESI (+ve): 393 $[M+H]^+$

c) 3-(8-Chloro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c) using the product of step b).

MS: ESI (+ve): 365 $[M-Na+2H]^+$

^{1}H NMR (DMSO-d6) δ 9.04 (1H, d), 7.96 (1H, dd), 7.78 (1H, dd), 7.55 (1H, d), 7.49 (1H, t), 7.26 (1H, d), 6.94-6.90 (2H, m), 4.45 (2H, dd), 2.31 (3H, s), 2.22 (3H, s)

Example 26

3-(7-Chloro-4-quinolinyl)-2-methyl-5-nitro-1*H*-indole-1-acetic acid, sodium salt

a) 7-Chloro-4-(2-methyl-5-nitro-1*H*-indol-3-yl)- quinoline, hydrochloride

A mixture of 2-methyl-5-nitroindole (1.34 g) and 4,7-dichloroquinoline (1.53 g) in NMP (1 ml) and 4M HCl in dioxane (0.1ml) was heated at 145 °C for 2 hours and at 160°C for 4 hours. After cooling the mixture triturated with ether and the solid collected to give the sub-title compound (2.72 g) as a green solid.

MS: ESI (+ve): 338 $[M-Cl]^+$

b) Ethyl 3-(7-chloro-4-quinolinyl)-2-methyl-5-nitro-1*H*-indole-1-acetate

A solution of the product from step a) (1.90 g), ethyl bromoacetate (0.68 ml) and caesium carbonate (3.3 g) in acetone (40 ml) was stirred for 24 hours. water was added and the mixture was extracted with ethyl acetate three times. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, petrol-acetone as eluent) gave the sub-title compound (1.19 g).

MS: ESI (+ve): 424 $[M+H]^+$

c) 3-(7-Chloro-4-quinolinyl)-2-methyl-5-nitro-1*H*-indole-1-acetic acid, sodium salt

The title compound was prepared by the method of Example 10 step c) using the product of step b).

MS: ESI (+ve): 396 $[M-Na+2H]^+$

^1H NMR (DMSO-d6) δ 9.03 (1H, d), 8.20 (1H, d), 8.05 - 8.00 (2H, m), 7.75 (1H, d), 7.67 - 7.55 (3H, m), 4.64 (2H, s), 2.28 (3H, s)

Example 27

5-chloro-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid

a) Methyl 5-chloro-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetate

5-Chloro-2-methylindole (0.16 g) and 4,8-dichloroquinoline (0.2 g) were suspended in NMP (0.5 ml) and heated in a microwave at 100W, 140°C for 60 minutes. When reaction was complete THF (5 ml) was added followed by sodium hydride 60% dispersion in oil (0.12 g). After 30 mins a solution of methyl bromoacetate (0.2 ml) in THF (1 ml) was added and the mixture stirred at room temperature for 24 hours. Ethyl acetate and saturated brine solution were added, the aqueous phase was separated and extracted with ethyl acetate. The combined organic solution was evaporated to leave a residue which was purified by silica gel chromatography using dichloromethane/ethyl acetate (9:1) to provide the sub-title product as an oil. (120 mg).

MS: APCI(+ve): 399/401/403 $[M+H]^+$

b) [5-chloro-3-(7-chloroquinolin-4-yl)-2-methyl-1*H*-indol-1-yl]acetic acid

A solution of lithium hydroxide monohydrate (0.26 g) in water (1 ml) was added to a solution of the product from step a) (** mg)in THF (4 ml) and and the solution was stirred at room temperature for 16 hours. Ethyl acetate and saturated brine solution were added, the aqueous phase was separated and extracted with ethyl acetate. The organic solution

was evaporated to leave a residue which was purified by Reverse Phase Preparative HPLC to give the product as a powder (34 mg).
MS: APCI(-ve): 383/385/387 $[M-H]^-$
^1H NMR (DMSO-d6) δ 9.0 (1H, d), 8.17 (1H, d), 7.69 (1H, d), 7.6 (2H, dd), 7.52 (1H, d), 7.19 (1H, dd), 7.12 (1H, d), 5.13 (2H, s), 4.45 (2H, q), 2.23 (3H, s)

Example 28

5-chloro-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

a) 5-chloro-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid, methyl ester
The sub-title product was prepared by the method of Example 27 step a), using 5-chloro-2-methylindole and 4-chloro-8-methylquinoline.
MS: APCI(+ve): 379/81 $[M+H]^+$

b) [5-chloro-2-methyl-3-(8-methylquinolin-4-yl)-1*H*-indol-1-yl]acetic acid
The title compound was prepared by the method of Example 27 step b), using the product of step a).
MS: APCI(-ve): 363/65 $[M-H]^-$
^1H NMR (DMSO-d6) δ 8,98 (1H, d), 7.64 (1H, d), 7.59 (1H, d), 7.52-7.44 (2H, m), 7.42 (1H, t), 7.18 (1H, dd), 7.06 (1H, d), 5.14 (2H, s), 2.79 (3H, s), 2.23 (3H, s)

Example 29

5-chloro-3-(6-methoxy-2-methyl-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid

a) 5-chloro-3-(6-methoxy-2-methyl-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid, methyl ester
The sub-title product was prepared by the method of Example 27 step a) using 5-chloro-2-methylindole and 4-chloro-6-methoxy-2-methylquinoline.
MS: APCI(+ve): 409/11 $[M+H]^+$

b) 5-chloro-3-(6-methoxy-2-methyl-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid
The title compound was prepared by the method of Example 27 step b), using the product of step a) to give the product as a powder.
MS: APCI(-ve): 393/95 $[M-H]^-$
^1H NMR (DMSO-d6) δ 7.92 (1H, d), 7.61 (1H, d), 7.39 (1H, d), 7.36 (1H, d), 7.19 (1H, t), 7.18 (1H, d), 6.93 (1H, d), 5.14 (2H, q), 3.65 (3H,s), 2.67 (3H, s), 2.23 (3H, s)

Example 30

5-Methoxy-2-methyl-3-(8-methyl-4-quinolinyl)-1H-indole-1-acetic acid, sodium salt

a) 4-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-8-methyl-quinoline

A mixture of 5-methoxy-2-methylindole (346 mg) and 4-chloro-8-trifluoromethylquinoline (380 mg) in NMP (1 ml) and 4M HCl in dioxane (0.1 ml) was heated at 140 °C for 50 min. Aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, petrol - acetone as eluent) to give the sub-title compound (465 mg).

MS: ESI (+ve): 303 $[M+H]^+$

b) Ethyl 5-methoxy-2-methyl-3-(8-methyl-4-quinolinyl)-1H-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b), using the product of step a).

MS: ESI (+ve): 389 $[M+H]^+$

c) 5-Methoxy-2-methyl-3-(8-methyl-4-quinolinyl)-1H-indole-1-acetic acid , sodium salt

The title compound was prepared by the method of Example 10 step c) using the product of step b).

MS: ESI (+ve): 361 $[M-Na+2H]^+$

^1H NMR (DMSO-d6) δ 8.96 (1H, d), 7.70 - 7.57 (2H, m), 7.47 - 7.35 (2H, m), 7.27 (1H, d), 6.73 (1H, d), 6.60 (1H, d), 4.47 (2H, s), 3.60 (3H, s), 2.79 (3H, s), 2.21 (3H, s)

Example 31

3-(7-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

a) 7-chloro-4-(5-fluoro-2-methyl-1*H*-indol-3-yl)- quinoline

A solution of 5-fluoro-2-methylindole (149mg) and 4,7-dichloroquinoline (198mg) in NMP (2 ml) and 4M hydogen chloride in dioxan (0.2 ml) was stirred at 140 °C overnight and then at 150 °C for 1 h. and evaporated. The residue was taken up in ethyl acetate, washed with brine (3x), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by silica chromatography using acetone/isohexane (2:8) as eluent to give the sub-title compound (250 mg).

b) 3-(7-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

A stirred suspension of the product from step a) (250 mg) and caesium carbonate (525 mg) in acetone (20 ml) was treated with methyl bromoacetate (300mg) and heated under reflux

overnight. The mixture was evaporated. The residue was taken up in ethyl acetate, washed with water and evaporated *in vacuo*. The residue was taken up in THF (20 ml), treated with a solution of lithium hydroxide (58 mg) in water (5 ml), stirred overnight and concentrated to remove most of the THF. The solution was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated to give a gum that was purified by reversed phase preparative HPLC gave the title compound (36 mg).

MS: APCI (+ve): 369 $[M+H]^+$

^1H NMR (DMSO-d6) δ 8.99 (1H, d), 8.22 (1H, d), 7.83 - 7.46 (4H, m), 7.17 - 6.77 (2H, m), 5.19 (2H, s), 2.30 (3H, s)

Example 32

5-fluoro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid

a) 4-(5-fluoro-2-methyl-1*H*-indol-3-yl)-8-(trifluoromethyl)-quinoline

The sub-title compound was prepared from 5-fluoro-2-methylindole and 4-chloro-8-trifluoromethylquinoline by the method of Example 31, step a).

b) 5-fluoro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid

The title compound was prepared from the product of step a, by the method of Example 31, step b).

MS: APCI (-ve): 401 $[M-H]^-$

^1H NMR (DMSO-d6) δ 9.11 (1H, d), 8.23 (1H, d), 7.99 (1H, d), 7.75 - 7.56 (3H, m), 7.04 (1H, m), 6.89 (1H, m), 5.17 (2H, s), 2.25 (3H, s)

Example 33

5-fluoro-2-methyl-3-(8-methyl-4-quinolinyl)- 1*H*-indole-1-acetic acid

a) 4-(5-fluoro-2-methyl-1*H*-indol-3-yl)-8-methyl- quinoline

The sub-title compound was prepared from 5-fluoro-2-methylindole and 4-chloro-8-methylquinoline by the method of Example 31, step a).

b) 5-fluoro-2-methyl-3-(8-methyl-4-quinolinyl)- 1*H*-indole-1-acetic acid

The title compound was prepared from the product of step a) by the method of Example 31, step b).

MS: APCI (+ve): 349 $[M+H]^+$

^1H NMR (DMSO-d6) δ 8.96 (1H, d), 7.65 - 7.54 (2H, m), 7.49 - 7.33 (3H, m), 6.93 (1H, m), 6.80 (1H, m), 4.64 (2H, d), 2.79 (3H, s), 1.89 (3H, s)

Example 34

2-methyl-3-(8-methyl-4-quinolinyl)-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid

a) methyl-4-[2-methyl-5-(trifluoromethyl)-1*H*-indol-3-yl]- quinoline

The sub-title compound was prepared from 2-methyl-5-(trifluoromethyl)-indole and 4-chloro-8-methylquinoline by the method of Example 31, step a).

b) 2-methyl-3-(8-methyl-4-quinolinyl)-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid

The title compound was prepared from the product from step a) by the method of Example 31, step b).

MS: APCI (+ve): 397 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 9.01 (1H, d), 7.71 (1H, d), 7.67 - 7.62 (1H, m), 7.55 - 7.48 (2H, m), 7.46 - 7.36 (3H, m), 4.98 (2H, s), 2.80 (3H, s), 2.25 (3H, s)

Example 35

3-(1,2-benzisothiazol-3-yl)-2-methyl-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid

a) 3-[2-methyl-5-(trifluoromethyl)-1*H*-indol-3-yl]- 1,2-benzisothiazole

The sub-title compound was prepared from 2-methyl-5-(trifluoromethyl)-indole 400 mg) and 3-chloro-1,2-benzisothiazole (338 mg) by the method of Example 31, step a) (400 mg)

b) 3-(1,2-benzisothiazol-3-yl)-2-methyl-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid

The title compound was prepared from the product of step a, by the method of Example 31, step b).

MS: APCI (-ve): 389 $[M-H]^-$

^{1}H NMR (DMSO-d6) δ 8.31 (1H, d), 7.86 (1H, d), 7.75 - 7.62 (3H, m), 7.55 - 7.41 (2H, m), 4.92 (2H, s), 2.45 (3H, s)

Example 36

3-(1,2-benzisothiazol-3-yl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

a) 3-(5-fluoro-2-methyl-1*H*-indol-3-yl)-1,2-benzisothiazole

The title compound was prepared from 5-fluoro-2-methylindole and 3-chloro-1,2-benzisothiazole by the method of Example 31, step a).

b) 3-(1,2-benzisothiazol-3-yl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared from the product of step a, by the method of Example 31, step b).

MS: APCI (-ve): 339 $[M-H]^-$

^1H NMR (DMSO-d6) δ 7.82 (1H, m), 7.57 (1H, m), 7.48 - 7.37 (1H, m), 7.26 (1H, m), 7.09 - 6.98 (2H, m), 6.65 (1H, d), 5.04 (2H, d), 2.41 (3H, s).

Example 37

3-(1,2-benzisothiazol-3-yl)-5-chloro-2-methyl-1*H*-indol-1-acetic acid

a) Methyl [3-(1,2-benzisothiazol-3-yl)-5-chloro-2-methyl-1*H*-indol-1-yl]acetate

The sub-title product was prepared by the method of Example 27 step a) using 5-chloro-2-methylindole and 3-chloro-1,2-benzisothiazole.

MS: APCI(+ve): 371/3 $[M+H]^+$

b) 3-(1,2-benzisothiazol-3-yl)-5-chloro-2-methyl-1*H*-indol-1-acetic acid

The title compound was prepared by the method of Example 27 step b) using the product of step a).

MS: APCI(-ve): 355/57 $[M-H]^-$

^1H NMR (DMSO-d6) δ 8.28 (1H, d), 7.87 (1H, d), 7.66 (1H, t), 7.51 (1H, t), 7.44 (1H, d), 7.34 (1H, s), 7.11 (1H, d), 4.59 (2H, s), 2.32 (3H, s)

Example 38

3-(1,2-benzisothiazol-3-yl)-4-methyl-1*H*-indole-1-acetic acid

a) 3-(4-methyl-1*H*-indol-3-yl)-1,2-benzisothiazole

The sub-title compound was prepared by the method of Example 16 step a) from 4 dimethyl indole and 3-chlorobenzisothiazole.

ES (+ve): 265 $[M+H]^+$

b) 3-(1,2-benzisothiazol-3-yl)-4-methyl-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 10 step b) using the product of step a).

c) 3-(1,2-benzisothiazol-3-yl)-4-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 10 step c) using the product of step b).

^1H NMR (DMSO-d6) δ 8.25(1H, d), 7.69(1H, d), 7.7(1H, s), 7.61 (1H, t), 7.53 (1H, t), 7.26 (1H, d), 7.11 (1H, t), 6.83 (1H, d), 4.74 (2H, s), 2.0 (3H,s).

Example 39

3-(1,2-benzisothiazol-3-yl)-2,4-dimethyl-1*H*-indole-1-acetic acid

a) 3-(2,4-dimethyl-1*H*-indol-3-yl)-1,2-benzisothiazole

The sub-title compound was prepared by the method of Example 16 step a) from 2,4 dimethyl indole and 3-chlorobenzisothiazole.

ES (+ve): 265 $[M+H]^+$

b) 3-(1,2-benzisothiazol-3-yl)-2,4-dimethyl-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 10 step b) using the product of step a).

ES (+ve): 364 $[M+H]^+$

c) 3-(1,2-benzisothiazol-3-yl)-2,4-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 10 step c) using the product of step b).

^{1}H NMR (DMSO-d6) δ 8.25(1H, d), 7.62(2H, m), 7.43(1H, t), 7.2 (1H, d), 6.97 (1H, t), 6.7 (1H, d), 4.46 (2H, s), 2.14 (3H,s), 1.86 (3H, s).

Example 40

3-(8-nitroquinolin-4-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 8-Nitro-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

2,5-Dimethylindole (300 mg) and 8-nitro-4-chloroquinoline (430 mg) were suspended in NMP (10 ml) containing 4M HCl in dioxane (2 drops) and maintained under a nitrogen atmosphere. The reaction was heated to 120°C with stirring for 8 hours. When cooled, the mixture was basified with saturated sodium hydrogen carbonate solution and extracted into ethyl acetate, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. The oil was purified by flash column chromatography using 2:1 isohexane/ethyl acetate as eluent to give the sub-title compound (560 mg).

MS: ESI (+ve): 318 $[M+H]^+$

b) 3-(8-nitroquinolin-4-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid, ethyl ester

The product of Example 40 stepa) (0.56 g) and caesium carbonate (0.686 g) were suspended in dry acetonitrile (20 ml) followed by addition of ethyl bromoacetate (0.235 ml) and maintained under a nitrogen atmosphere. The reaction was heated to reflux for 6 hours. The solvents were evaporated under reduced pressure. The residue was sujected to

flash column chromatography using 2:1 isohexane/ethyl acetate as eluent to give the sub-title compound (50m g).
MS: ESI (+ve): 404 $[M+H]^+$

c) 3-(8-nitroquinolin-4-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid
The product of Example 40 step b) (0.50 g) was suspended in THF (10 ml) and to it added 1M sodium hydroxide (1.24 ml) for the mixture to be stirred overnight at room temperature to complete the reaction. The solution was evaporated to dryness and purified by Reverse Phase Preparative HPLC to give the title compound as a yellow solid (0.31 g).

MS: ESI (+ve): 376 $[M+H]^+$
^{1}H NMR (DMSO-d6) δ 9.05-9.03 (1H, d), 8.25-8.23 (1H, d), 8.03-8.00 (1H, d), 7.69-7.63 (2H, m), 7.29 (1H, d), 6.93 (2H, dd), 4.65-4.53 (2H, q), 2.29 (3H, s), 2.24 (3H, s)

Example 41
3-(8-cyano-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid
a) 8-Cyano-(2,5-dimethyl-1*H*-indol-3-yl)quinoline
The sub-title compound was prepared by the method of Example 40 step a, using 2,5-dimethyl indole and 8-cyano-4-chloroquinoline and 1 molar equivalent of 4M HCl in dioxane.
MS: ESI (+ve): 298 $[M+H]^+$

b) 3-(8-cyano-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid, ethyl ester
The sub-title compound was prepared by the method of Example 40 step b, using the product of step a.
MS: ESI (+ve): 384 $[M+H]^+$

c) 3-(8-cyano-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid
The title compound was prepared by the method of Example 40 step c, using the product of step b.
MS: ESI (+ve): 356 $[M-H]^-$
^{1}H NMR (DMSO-d6) δ 9.10-9.09 (1H, d), 8.38-8.35 (1H, d), 8.12-8.09 (1H, d), 7.69-7.62 (2H, m), 7.27-7.25 (1H, d), 6.95-6.92 (2H, dd), 4.49-4.37 (2H, q), 2.29 (3H, s), 2.21(3H, s)

Example 42
2,5-dimethyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) 8-methanesulphonyl-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

The sub-title compound was prepared by the method of Example 40 step a, using 2,5-dimethyl indole and 8-methanesulphonyl-4-chloroquinoline.

MS: ESI (+ve): 351 [M+H]

b) 2,5-dimethyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 40 step b, using the product of step a.

MS: ESI (+ve): 437 $[M+H]^+$

c) 2,5-dimethyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 40 step c, using the product of step b.

MS: ESI (+ve): 407 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 9.13-9.12 (1H, d), 8.43-8.41 (1H, d), 8.14-8.11 (1H, d), 7.74-7.70 (1H, m), 7.64-7.63 (1H, d), 7.31-7.29 (1H, d), 6.95-6.94 (2H, dd), 4.63-4.54 (2H, q), 3.67 (3H, s), 2.28 (3H, s), 2.23(3H, s)

Example 43

2,5-dimethyl-3-(1,5-naphthyridin-4-yl)-1*H*-indole-1-acetic acid

a) 4-(2,5-dimethyl-1*H*-indol-3-yl)-1,5-naphthyridine

The sub-title compound was prepared by the method of Example 40 step a), using 2,5-dimethyl indole and 8-methanesulphonyl-4-chloroquinoline.

MS: ESI (+ve): 274 $[M+H]^+$

b) 2,5-dimethyl-3-(1,5-naphthyridin-4-yl)-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 40 step b), using the product of step a).

MS: ESI (+ve): 360 $[M+H]^+$

c) 2,5-dimethyl-3-(1,5-naphthyridin-4-yl)-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 40 step c), using the product of step b).

MS: ESI (+ve): 332 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 9.00-8.99 (1H, d), 8.93-8.91 (1H, m), 8.46-8.43 (1H, dd), 7.79-7.72 (2H, m), 7.23-7.20 (1H, d) 7.09 (1H, m), 6.90-6.87 (1H, dd), 4.48 (2H, s), 2.30 (3H, s), 2.21(3H, s)

Example 44

3-[8-(difluoromethoxy)-4-quinolinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione.

2,2-Dimethyl-1,3-dioxane-4,6-dione (100 g) was heated in trimethylorthoformate (500 ml) at 100 °C for 2 h. The solution was evaporated under reduced pressure to give an oil. The oil was triturated with 1:1 isohexane/diethyl ether (400 ml) and the solid was filtrated and dried in vacuo to give the sub-title compound (99.8 g).

^{1}H NMR ($CDCl_3$) δ 8.15 (1H, s), 4.28 (3H, s), 1.77-1.71 (6H, s).

b) 8-(difluoromethoxy)-4-quinolinol

2-difluoromethoxyaniline (7.63 g) and the product from step a) were stirred in acetonitrile (100 ml) overnight. The solvent was removed by evaporation and the solid triturated with 4:1 isohexane/diethyl ether (200 ml) before filtering to give a light green solid. The solid was added portionwise to refluxing diphenylether (120 ml) and continued heating for a further 10 minutes before cooling. The solution was poured into isohexane (600 ml) and the solid filtered off to give the title compound (12.0 g).

^{1}H NMR (DMSO-d6) δ 11.54 (1H, bs), 7.96-7.93 (1H, d) 7.84-7.82 (1H, m), 7.54-7.52 (1H, d), 7.42-7.35 (1H, m), 7.16-6.99 (1H, m), 6.11-6.08 (1H, d).

c) 8-(difluoromethoxy)-4-chloroquinoline

The product from step b) was heated to reflux in phosphorus oxychloride (80 ml) for 1 hour. The reagent was evaporated under reduced pressure to give an oil which was carefully poured into a mixture of ice/880 ammonia solution (400 ml) and stirred for 30 minutes. The solid was filtered off and dried in vacuo to give the sub-title compound (6.80 g).

MS: ESI (+ve): 230 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 8.92-8.91 (1H, d) 8.13-8.11 (1H, d), 7.91-7.89 (1H, d), 7.81-7.70 (1H, t), 7.69-7.65 (1H, d), 7.65-7.27 (1H, bt)

d) 8-(difluoromethoxy)-(2,5-dimethyl-1*H*-indol-3-yl)quinoline

The sub-title compound was prepared by the method of Example 40 step a), using 2,5-dimethyl indole and 8-difluoromethoxy-4-chloroquinoline.

MS: ESI (+ve): 339 [M+H]

e) 3-[8-(difluoromethoxy)-4-quinolinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 40 step b), using the product of step d).

MS: ESI (+ve): 425 [M+H]

f) 3-[8-(difluoromethoxy)-4-quinolinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 40 step c) using the product of step e).

MS: ESI (+ve): 397 $[M+H]^+$

^{1}H NMR (DMSO-d6) δ 9.00-8.99 (1H, d), 7.69-7.66 (1H, m), 7.57-7.49 (4H, m) 7.32-7.30 (1H, d), 6.95-6.93 (1H, dd), 4.72-4.63 (2H, q), 2.28 (3H, s), 2.21(3H, s).

Example 45

5-Amino-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid

a) Ethyl 5-amino-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetate

A suspension of the product from Example 26, step b) (1.60 g) and 5% platinum on carbon 910 mg) in ethanol was stirred under 2 atmospheres of hydrogen for 16 h. The mixture was filterd, evaporated and purified by silica chromatography (petrol-acetone as eluent) to give the sub-title compound (1.17 g).

MS: ESI (+ve): 435 $[M+H]^+$

b) 5-Amino-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid

The sub-title compound was prepared by the method of Example 15 step c) using the product of step b).

MS: ESI (+ve): 366 $[M+H]^+$, 100%.

^{1}H NMR (DMSO-d6) δ 8.95 (1H, d), 8.12 (1H, d), 7.82 (1H, d), 7.56 (1H, dd), 7.44 (1H, d), 7.13 (1H, d), 6.50 (1H, dd), 6.34 (1H, d), 4.72 (2H, s), 2.19 (2H, s), 1.91 (3H, s)

Example 46

3-(7-Chloro-4-quinolinyl)-2-methyl-5-[(methylsulfonyl)amino]-1*H*-indole-1-acetic acid

a) Ethyl 3-(7-chloro-4-quinolinyl)-2-methyl-5-[(methylsulfonyl)amino]-1*H*-indole-1-acetate

Methane sulfonyl chloride (70 µl) was added to a solution of the product from Example 46 step a) and triethylamine (0.13 ml) in dichloromethane (3 ml) at 0°C and stirred at 20°C for 1h. Water was added and the mixture was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), evaporated and purified by silica chromatography (petrol - acetone) to give the sub-title compound (238 mg).
MS: ESI (+ve): 472 $[M+H]^+$, 100%.

b) 3-(7-Chloro-4-quinolinyl)-2-methyl-5-[(methylsulfonyl)amino]-1*H*-indole-1-acetic acid
The title compound was prepared by the method of Example 15 step c), using the product of step a). M.p. 195-8 °C.
MS: ESI (+ve): 444 $[M+H]^+$
^1H NMR (DMSO-d6) δ 13.19 (1H, s), 9.24 (1H, s), 9.01 (1H, d), 8.17 (1H, d), 7.75 (1H, d), 7.61 - 7.49 (3H, m), 7.10 (1H, dd), 7.02 (1H, d), 5.13 (2H, s), 2.82 (3H, s), 2.26 (3H, s)

Example 47
5-(Acetylamino)-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid
a) Ethyl 5-(Acetylamino)-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetate
Acetyl chloride (60 µl) was added to a solution of the product from Example 46 step a) and triethylamine (0.13 ml) in dichloromethane (3 ml) at 0°C and stirred at 20 °C for 1 hour. Water was added and the mixture was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, ethyl acetate as eluent) to give the sub-title compound (290 mg). M.p. 281-4°C.
MS: ESI (+ve): 436 $[M+H]^+$

b) 5-(Acetylamino)-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid
The title compound was prepared by the method of Example 15 step c), using the product of step a) .
MS: ESI (+ve): 408 $[M+H]^+$
^1H NMR (DMSO-d6) δ 13.15 (1H, s), 9.72 (1H, s), 9.00 (1H, d), 8.17 (1H, d), 7.75 (1H, d), 7.59 (1H, dd), 7.52 - 7.36 (4H, m), 5.10 (2H, s), 2.25 (3H, s), 1.95 (3H, s)

Example 48
3-(1,2-Benzisothiazol-3-yl)-7-chloro-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid
a) 7-Chloro-5-fluoro-2,4-dimethyl-3-methylthio-1*H*-indole
A stirred solution of 2-chloro-4-fluoro-5-methylaniline (1.655 g) in methylene chloride (100 ml) under nitrogen was treated at –65°C with a solution of ^{t}butylhypochlorite (1.126

g) in methylene chloride (5 ml), stirred at –65 °C for 10 min, treated at –65°C with a solution of methylthioacetone (1.080g) in methylene chloride (5 ml) stirred at –65°C for 1 hour, treated at –65°C with triethylamine (1.05 g) and allowed to reach ambient temperature. The solution was washed, dried ($MgSO_4$) and evaporated. The residue was purified by silica chromatography using 25% acetone in isohexane as eluent to give the sub-title compound (1.704 g).

MS: APCI (-ve): 242 $[M-H]^-$

^1H NMR (DMSO-d6) δ 11.67 (1H, s), 7.07 (1H, d), 2.71 (3H, d), 2.48 (3H, s), 2.19 (3H, s).

b) 7-Chloro-5-fluoro-2,4-dimethyl-1*H*-indole

A solution of the product from part a) (1.134 g) and thiosalicylic acid (1.435 g) in trifluoroacetic acid (50ml) was stirred at 60 °C for 2 h and evaporated. The residue was taken up in methylene chloride, washed with 1M aqueous sodium hydroxide solution followed by water, dried ($MgSO_4$) and evaporated. The residue was purified by silica chromatography using 10% ethyl acetate in isohexane as eluent to give the sub-title compound (817 mg).

MS: ESI : MW197, BP 196

^1H NMR (DMSO-d6) δ 11.25 (1H, s), 6.97 (1H, d), 6.28 (1H, q), 2.40 (3H, d), 2.30 (3H, d)

c) 3-(1,2-Benzisothiazol-3-yl)-7-chloro-5-fluoro-2,4-dimethyl-1*H*-indole

A solution of the product from step b) (200 mg) and 3-chloro-1,2-benzisothiazole (171mg) in NMP (2ml) and 4M hydogen chloride in dioxan (0.2 ml) was stirred at 140°C overnight and then at 150 °C for 1 hour. and evaporated. The residue was taken up in ethyl acetate, washed with brine (3X), dried ($MgSO_4$) and evaporated. The residue was purified by silica chromatography using 20% acetone in isohexane as eluent to give the title compound (219 mg).

MS: APCI (-ve): 331 $[M+H]^+$

^1H NMR (DMSO-d6) δ 8.33 (1H, s), 8.01 (1H, d), 7.66 (1H, d), 7.56 (1H, t), 7.39 (1H, t), 6.99 (1H, d), 2.34 (3H, s), 1.79 (3H, d).

d) 3-(1,2-Benzisothiazol-3-yl)-7-chloro-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid

A stirred suspension of the product from step c) (205 mg) and caesium carbonate (493 mg) in acetone (20 ml) was treated with methyl bromoacetate (217 mg) and heated under reflux overnight. The mixture was evaporated. The residue was taken up in ethyl acetate, washed and evaporated. The residue was taken up in THF (20 ml), treated with a solution of lithium hydroxide (26 mg) in water (5 ml), stirred overnight, treated with more lithium

hydroxide (78 mg), stirred for 2 hours and concentrated to remove most of the THF. The solution was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The washed and dried ($MgSO_4$) extracts were evaporated to give a gum that was purified by reversed phase preparative HPLC on 19x50 mm Xterra C8 column using 5 to 90% acetonitrile in 0.2% aqueous 0.880 ammonia over 7 mins at 20 ml/min. The clean eluents were freeze dried to give the title compound (168 mg).

MS: APCI (-ve): 387 $[M+H]^+$

^1H NMR (DMSO-d6) δ 8.28 (1H, d), 7.64 (1H, ddd), 7.58 (1H, d), 7.47 (1H, ddd), 7.04 (1H, d), 4.97 (2H, dd), 2.08 (3H, s), 1.65 (3H, d).

Example 49

3-(1,2-Benzisothiazol-3-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid

a) 5-Fluoro-2,4-dimethyl-1*H*-indole

A stirred suspension of 10% palladium on carbon (200 mg) in ethanol (50 ml) was treated with a solution of ammonium formate (2.3 g) in water (2 ml), stirred for 1 min, treated with a solution the the product from Example 48, part b (721 mg) in ethanol (10 ml), stirred for 2 days, treated with more 10% palladium on carbon (500 mg), stirred at 40°C for 2 hours and filtered. The solids were washed with ethanol and the combined filtrates were evaporated. The residue was taken in ether, washed, dried ($MgSO_4$) and evaporated to give the sub-title compound.

MS: ESI : 163$[M+H]^+$

BP 162°C

^1H NMR (DMSO-d6) δ 7.82 (1H, s), 7.04 - 7.01 (1H, m), 6.82 (1H, dd), 6.21-6.21 (1H, m), 2.45 (3H, s), 2.40 - 2.40 (3H, m).

b) 3-(1,2-Benzisothiazol-3-yl)-5-fluoro-2,4-dimethyl-1*H*-indole

The sub-title compound was prepared from the product of step a) (165 mg) and 3-chloro-1,2-benzisothiazole (171 mg) by the method of Example 48, step c (93 mg).

MS: APCI (-ve): 297 $[M+H]^+$

^1H NMR (DMSO-d6) δ (1H, s), 8.00 (1H, d), 7.69-7.66 (1H, m), 7.57-7.51 (1H, m), 7.39-7.34 (1H, m), 7.03-6.99 (1H, m), 6.85 (1H, t), 2.13 (3H, s), 1.83 (3H, d).

c) 3-(1,2-Benzisothiazol-3-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid

The title compound was prepared from the product from step b, by the method of Example 48, step d.

MS: APCI (-ve): 353 $[M-H]^-$

^{1}H NMR (DMSO-d6) δ 8.26 (1H, d), 7.64-7.59 (2H, m), 7.45 (1H, ddd), 7.28-7.25 (1H, m), 6.94-6.89 (1H, m), 4.70 (2H, s), 2.13 (3H, s), 1.74 (3H, d)

Example 50

3-(7-Chloro-4-quinolin-4-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid

a) 3-(7-Chloro-4-quinolin-4-yl)-5-fluoro-2,4-dimethyl-1*H*-indole

The sub-title compound was prepared from the product of Example 49, step a) and 4,7-dichloroquinoline by the method of Example 48, step c).

MS: APCI (-ve): 331 $[M+H]^+$

^{1}H NMR ($CDCl_3$) δ 8.96 (1H, d), 8.46 (1H, s), 8.18 (1H, d), 7.61 (1H, d), 7.40 - 7.36 (2H, m), 7.19 - 7.15 (1H, m), 6.93 (1H, t), 2.18 - 2.18 (3H, m), 1.71 (3H, d)

b) 3-(7-Chloro-4-quinolin-4-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid

The title compound was prepared from the product from step a), by the method of Example 48, step d). Purification by reversed phase preparative HPLC to give the title compound.

MS: APCI (-ve): 381 $[M-H]^-$

^{1}H NMR (DMSO-d6) δ 8.99 (1H, d), 8.16 - 8.15 (1H, m), 7.56 - 7.55 (2H, m), 7.51 (1H, d), 7.37 - 7.33 (1H, m), 6.95 (1H, t), 4.94 (2H, s), 2.06 (3H, s), 1.61 (3H, d).

Example 51

5-Chloro-2-methyl-3-(8-quinolinyl)-1*H*-indole-1-acetic acid

a) 5-chloro-3-iodo-2-methyl-1*H*-indole-1-acetic acid

A solution of iodine (14 g) was added dropwise over 10 mins to a solution of the 5-chloro-2-methyl indole (8.3 g) and 4-chlorothiophenol (8 g) in ethanol (250 ml) and stirred for 1 hour. The mixture was concentrated *in vacuo* and the residue was treated with diethyl ether to give the sub-title compound as an off white solid (9.9 g)

MS: APCI (+ve): 291 $[M+H]^+$

b) 5-chloro-3-iodo-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

The product of step a) (9.9 g) was dissolved in DMF (60 ml), treated with sodium hydride (1.65 g) and stirred for 30 min. Ethyl bromoacetate (6.9 ml) was added and the reaction mixture stirred for a further 30 min. The reaction was quenched with dilute acetic acid (300 ml), extacted EtOAc (x3), then washed water, brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica chromatography eluting with EtOAc/hexane (25:75 v/v) to afford the sub-title compound (8.5 g).

MS: APCI (+ve): 379 $[M+H]^+$

c) 5-Chloro-2-methyl-3-(8-quinolinyl)-1*H*-indole-1-acetic acid

The product of part b (250mg), 7-quinoline boronic acid (114mg), 2M sodium bicarbonate (0.7ml), toluene, ethanol, tetrakis palladium triphenyl phosphine (0) and lithium chloride were heated at reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, purified using amine resin and then by reverse phase preparative HPLC to give the title compound as a white solid.

^{1}H NMR (DMSO-d6) δ 8.81(1H, s), 8.43(1H,d), 8.02-7.97(1H,m), 7.78-7.7(1H,m), 7.39(1H,d), 7.04(2H,m), 4.67(2H,s), 2.2(3H,s).

Example 52

5-chloro-2-methyl-[3,5'-bi-1*H*-indole]-1-acetic acid

a) 5-chloro-2-methyl-[3,5'-bi-1*H*-indole]-1-acetic acid, ethyl ester

The product of Example 51 part b (200 mg), 5-indole boronic acid (100 mg), potassium carbonate (0.73g), acetone (6 ml), water (3 ml), palladium acetate (12 mg) and tri(*o*-tolyl) phosphine (30mg) were heated at 90°C for 4 hours. The reaction mixture was concentrated *in vacuo*, purified by silica chromatography eluting with hexane:EtOAc (7:3) to give the sub-title compound (140 mg).

MS (APCI$^+$) 369 $[M+H]^+$

b) 5-chloro-2-methyl-[3,5'-bi-1*H*-indole]-1-acetic acid

The product from part a) (121 mg) was treated with NaOH (0.3 ml), THF (3 ml) and ethanol (1ml), stirred for 1 h, concentrated *in vacuo*. The residue was dissolved in ethyl acetate and water. The aqueous phase was concentrated *in vacuo* and further purified by preparative reverse phase chromatography to give the title compound as a white solid (47 mg).

^{1}H NMR (DMSO-d6) δ 7.59-7.23(5H, m), 7.18(1H,d), 7.0(1H,d), 6.47(1H,s), 4.52(2H,s), 7.04(2H,m), 2.39(3H,s).

Example 53

3-benzo[*b*]thien-3-yl-5-chloro-2-methyl-1*H*-indole-1-acetic acid

a) 3-benzo[*b*]thien-3-yl-5-chloro-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

The product of Example 51 part b (600 mg), benzothiaphene-3-boronic acid (420 mg), potassium carbonate (35mg), acetone (18 ml), water (9 ml) and palladium acetate tri (*o*-tolyl) phoshine (97 mg) were heated at 90 °C for 2 h. The reaction mixture was concentrated *in vacuo*, purified (SiO_2 chromatography), eluting with hexane:ether (8:2 v/v)

to give the sub-title compound (270 mg), then hexane:methanol:acetic acid (1:1:0.5 v/v) to give the crude title compound. This was further purified by preparative reverse phase HPLC to give the title compound (30 mg).

b) 3-benzo[*b*]thien-3-yl-5-chloro-2-methyl-1*H*-indole-1-acetic acid

The sub-title compound was prepared by the method of Example 52 step b) using the product of step a).

^{1}H NMR (DMSO-d6) δ 8.07 (1H, dd), 7.63 (1H,s), 7.53-7.37 (4H,m), 7.18 (1H,d), 7.05 (1H,dd), 4.63 (2H,s) and 2.28 (3H,s).

Example 54

2,5-Dimethyl-3-thieno[2,3-*d*]pyrimidin-4-yl 1*H*-indole-1-acetic acid

a) 4-(2,5-Dimethyl-1*H*-indol-3-yl)-thieno[2,3-*d*]pyrimidine, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a) using 2,5-dimethylindole and 4-chloro-thieno[2,3-*d*]pyrimidine.

MS: ESI (+ve): 280 $[M-Cl]^+$

b) Ethyl 2,5-dimethyl-3-thieno[2,3-*d*]pyrimidin-4-yl 1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b) using the product of step a).

MS: ESI (+ve): 366 $[M+H]^+$, 100%.

c) 2,5-Dimethyl-3-thieno[2,3-*d*]pyrimidin-4-yl 1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 15 step c) using the product of step b).

MS: ESI (+ve): 338 $[M+H]^+$, 100%.

^{1}H NMR (DMSO-d6) δ 9.09 (1H, s), 9.09 (1H, s), 7.90 (1H, d), 7.35 - 7.26 (3H, m), 4.70 (2H, s), 2.45 (3H, s), 2.34 (3H, s)

Example 55

5-Chloro-3-(7-chloro-4-quinolinyl)-2-(hydroxymethyl)-1*H*-indole-1-acetic acid

1-Bromo-2,5-pyrrolidinedione (0.26 g) was added to a solution of the product from Example 27 step b) (0.5 g) in DMF (5 ml) and the solution stirred at room temperature for 20 mins. Water (5 ml) was added and the mixture stirred for a further 30 mins. The reaction was diluted with further water (50 ml), extracted with ethyl acetate, dried ($MgSO_4$) and filtered. The filtrate was evaporated *in vacuo* and the residue purified by

reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (48 mg).
MS (APCI-) 399 $[M-H]^-$
^{1}H NMR (DMSO-d6) δ 9.01 (1H, d), 8.17 (1H, s), 7.79 (1H, d), 7.59 (3H, m), 7.23 (1H, d), 7.13 (1H, s), 5.01 (2H, s), 4.44 (2H, dd)

Example 56
5-Chloro-3-(7-chloro-4-quinolinyl)-2-(methoxymethyl)-1*H*-indole-1-acetic acid
1-Bromo-2,5-pyrrolidinedione (0.26 g) was added to a solution of the product from Example 27 step b) (0.5 g) in DMF (5 ml) and methanol (2 ml), and the solution stirred for 1 h. The solvents were evaporated *in vacuo* and the residue purified by reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid, which was filtered and dried to yield the title compound as a white solid (48 mg).
MS (APCI-) 413 $[M-H]^-$
^{1}H NMR (DMSO-d6) δ 9.02 (1H, d), 8.18 (1H, s), 7.71 (1H, d), 7.65 (1H, d), 7.61 (1H, d), 7.52 (1H, d), 7.27 (1H, d), 7.15 (1H, s), 5.12 (2H, s), 4.42 (2H, dd), 3.08 (3H, s)

Example 57
2-[(Acetyloxy)methyl]-5-chloro-3-(7-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid
1-Bromo-2,5-pyrrolidinedione (50 mg) was added to a solution of the product from Example 27 step b) (0.1 g) in 1,2-dichloroethane (5 ml) and acetic acid (2 ml), and the solution stirred for 1 hour. The solvents were evaporated *in vacuo* and the residue purified by reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid, whci was filtered and dried to yield the title compound as a white solid (40 mg).
MS (APCI-) 441 $[M-H]^-$
^{1}H NMR (DMSO-d6) δ 9.03 (1H, d), 8.18 (1H, s), 7.71 (1H, d), 7.64 (1H, s), 7.62 (1H, s), 7.55 (1H, d), 7.30 (1H, d), 7.17 (1H, s), 5.20 (2H, s), 5.10 (2H, dd), 1.91 (3H, s)

Example 58
5-Chloro-3-(7-chloro-4-quinolinyl)-2-[(methylamino)methyl]-1*H*-indole-1-acetic acid
1-Bromo-2,5-pyrrolidinedione (125 mg) was added to a solution of the product from Example 27 step b) (250 mg) in NMP (0.5 ml) and dichloromethane (5ml), and the solution stirred for 30 min. 2M methylamine/THF (3.25 ml) was then added and the solution stirred for 1 hour. The mixture was diluted with dichloromethane (20ml), washed with saturated aqueous sodium bicarbonate and water. The organic layer was dried

($MgSO_4$), filtered, evaporated *in vacuo* and the residue purified by reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid, filtered off and dried to yield the title compound as a white solid (60 mg).

MS (APCI-) 411 $[M-H]^-$

^1H NMR (DMSO-d6) δ 9.04 (1H, d), 8.19 (1H, s), 7.68 (1H, d), 7.65 (1H, d), 7.59 (2H, m), 7.32 (1H, d), 7.14 (1H, s), 4.87 (2H, dd), 4.21 (2H, dd), 2.27 (3H, s)

Example 59

5-Chloro-3-(7-chloro-5,8-dihydro-4-quinolinyl)-2-(1-pyrrolidinylmethyl)-1*H*-indole-1-acetic acid

1-Bromo-2,5-pyrrolidinedione (165 mg) was added to a solution of the product from Example 27 (0.3 g) in DMF (3 ml), and the solution stirred for 10 min. Pyrrolidine (0.5 ml) was then added and the mixture stirred for a further 30 min. The solvents were evaporated *in vacuo* and the residue purified by reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid which was filtered off and dried to yield the title compound as a white solid (70 mg).

MS (APCI+) 454 $[M+H]^+$

^1H NMR (DMSO-d6) δ 9.03 (1H, d), 8.18 (1H, s), 7.66 (1H, d), 7.57 (3H, m), 7.26 (1H, d), 7.09 (1H, s), 5.00 (2H, s), 3.97 (2H, dd), 2.46 (4H, m), 1.56 (4H, m)

Example 60

5-Chloro-3-(7-chloro-4-quinolinyl)-2-[(methylthio)methyl]-1*H*-indole-1-acetic acid

1-Bromo-2,5-pyrrolidinedione (0.11 g) was added to a solution of the product from Example 27 step b) (0.2 g) in DMF (2 ml), and the solution stirred for 10 min. Sodium thiomethoxide (43 mg) was then added and the mixture stirred for a further 3 hours. The solvents were evaporated *in vacuo* and the residue purified by reverse phase HPLC. The residue was triturated with ether to give a solid, which was filtered and dried to yield the title compound as a white solid (40 mg).

MS (APCI+) 429 $[M+H]^+$

^1H NMR (DMSO-d6) δ 9.02 (1H, d), 8.18 (1H, s), 7.67 (1H, d), 7.58 (3H, m), 7.24 (1H, d), 7.05 (1H, s), 5.18 (2H, s), 3.85 (2H, dd), 1.69 (3H, s)

Example 61

5-Chloro-3-(7-chloro-4-quinolinyl)-2-[(methylsulfonyl)methyl]-1*H*-indole-1-acetic acid

1-Bromo-2,5-pyrrolidinedione (0.11g) was added to a solution of the product from Example 27 step b) (0.2 g) in DMF (5 ml), and the solution stirred for 10 min. Sodium methanesulfinate (63 mg) was then added and the mixture stirred for a further 3 hours. The solvents were evaporated *in vacuo* and the residue purified by reverse phase HPLC. After evaporation *in vacuo* the oily residue was treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (50 mg).

MS (APCI+) 461 $[M+H]^+$

^1H NMR (DMSO-d6) δ 9.02 (1H, d), 8.18 (1H, s), 7.67 (1H, d), 7.61 (1H, d), 7.57 (2H, m), 7.27 (1H, d), 7.01 (1H, s), 5.18 (2H, s), 4.74 (2H, dd), 3.57, 2.91 (3H, s)

Example 62

3-(7-Chloro-4-quinolinyl)-4-methoxy-2-methyl-1*H*-indole-1-acetic acid

a) 4-(4-Methoxy-2-methyl-1*H*-indol-3-yl)-8-methyl-quinoline, hydrochloride

The sub-title compound was prepared by the method of Example 15 step a) using 4-methoxy-2-methylindole and 4,7-chloroquinoline.

MS: ESI (+ve): 324 $[M-Cl]^+$

b) Ethyl 3-(7-chloro-4-quinolinyl)-4-methoxy-2-methyl-1*H*-indole-1-acetate

The sub-title compound was prepared by the method of Example 15 step b) using the product of step a).

MS: ESI (+ve): 409 $[M+H]^+$

c) 3-(7-Chloro-4-quinolinyl)-4-methoxy-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 15 step c) using the product of step b).

MS: ESI (+ve): 381 $[M+H]^+$, 100%.

1H NMR (300MHz, DMSO-d6) δ 13.12 (1H, s), 8.93 (1H, d), 8.10 (1H, d), 7.62 (1H, d), 7.51 (1H, dd), 7.42 (1H, d), 7.16 - 7.07 (2H, m), 6.55 (1H, d), 5.08 (2H, s), 3.36 (3H, s), 2.13 (3H, s)

Example 63

5-chloro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) 4-(5-chloro-2-methyl-3*H*-indol-3-yl)-8-(trifluoromethyl)quinoline

The sub-title compound was prepared by the method of Example 10 step a) using 5-chloro-2-methylindole and 4-chloro-6-trifluoromethylquinoline.

MS: ESI (+ve): 435/37 $[M+H]^+$

b) 5-chloro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 10 step b) using the product of step a) to give an oil 0.5 g which was used in step c) without further purification.

c) 5-chloro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The title compound was prepared by the method of Example 27 step b) using the product of step b).

MS: APCI(-ve): 419/21[M-H]$^-$

^{1}H NMR (DMSO-d6) δ 9.1 (1H, d), 8.24 (1H, d), 7.96 (1H, d), 7.69 (1H, t), 7.66-7.61 (2H, m), 7.2 (1H, d), 7.14 (1H, s) 5.16 (2H, dd), 2.28 (3H, s).

Example 64

5-Cyano-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

a) 5-Cyano-2-methyl-1*H*-indole

5-Cyano-2-methyl-3-methylthio-1*H*-indole was prepared from 4-cyanoaniline by the method of example 48, part a) and used to prepare the subtitle compound by the method of example 48, part b).

^{1}H NMR (DMSO-d6) δ 11.53 (s,1H), 7.91 (1H, s), 7.42 (1H, d), 7.33 (1H, d), 6.27 (1H, s), 2.41 (3H, s).

b) Methyl 5-Cyano-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetate

A solution of the product from part a) (468 mg) and 4-chloro-8-methylquinoline (533 mg) in NMP (1 ml) and 4M hydogen chloride in dioxan (1 ml) was stirred at 150°C overnight and evaporated. The residue was taken up in ethyl acetate, washed with brine (3 x), dried ($MgSO_4$) and evaporated. The residue was taken up in acetone (20 ml) treated with cesium carbonate (2.44 g) followed by methyl bromoacetate (0.64 ml), heated under reflux overnight and evaporated. The residue was taken up in ethyl acetate, washed with brine (3 x), dried ($MgSO_4$) and evaporated. The residue was purified by silica chromatography using 20% acetone in isohexane as eluent to give the subtitle compound.

^{1}H NMR ($CDCl_3$) δ 9.04 (1H, d), 7.62-7.59 (2H, m), 7.53-7.48 (2H, m), 7.39-7.34 (3H, m), 4.97 (2H, s), 3.84 (3H, s), 2.91 (3H, s), 2.31 (3H, s)

c) 5-Cyano-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

The product from step b) was taken up in THF (10 ml) treated with a solution of lithium hydroxide (252 mg) in water (10 ml) and stirred for 1 hour. The solution was concentrated to remove the THF and acidified with saturated aqueous potassium hydrogen sulphate. The solid was collected by filtration, washed with water, washed with a little cold propan-2-ol, washed with a little cold ether and dried to give the title compound as a yellow/ orange solid (606 mg).

^{1}H NMR (DMSO-d6) δ 9.01 (1H, d), 7.79 (1H, d), 7.66 (1H, d), 7.58 - 7.41 (5H, m), 5.23 (2H, s), 2.81 (3H, s), 2.25 (3H, s)

MS: ASI (-ve): 354 [M-1]

Example 65

5-Cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) Methyl 5-Cyano-2-methyl-3-(8-trifluoromethyl-4-quinolinyl)-1*H*-indole-1-acetate

The sub-title compound was prepared from the product of example 55, step a) and 4-chloro-8-trifluoromethylquinoline by the method of example 55, step b).

^{1}H NMR ($CDCl_3$) δ 9.17 (1H, d), 8.13 (1H, d), 7.91 (1H, d), 7.56 - 7.49 (4H, m), 7.38 (1H, d), 4.99 (2H, s), 3.85 (3H, s), 2.33 (3H, s)

b) 5-Cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The title compound was prepared from the product from step a) by the method of example 55, step c).

^{1}H NMR (DMSO-d6) δ 13.32 (1H, s), 9.14 (1H, d), 8.24 (1H, d), 7.93 (1H, d), 7.81 (1H, d), 7.73-7.68 (3H, m), 7.58 (1H, dd), 5.27 (2H, s), 2.27 (3H, s)

MS: APCI (-ve): 408 [M-1]

Example 66

3-(7-Chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) Methyl 5-Cyano-2-methyl-3-(8-trifluoromethyl-4-quinolinyl)-1*H*-indole-1-acetate

The sub-title compound was prepared from the product of example 55, step a) and 4,7-dichloroquinoline by the method of example 55, step b).

^{1}H NMR ($CDCl_3$) δ 9.03 (1H, d), 8.46 (1H, s), 7.72 (1H, d), 7.60 (2H, d), 7.55 - 7.52 (3H, m), 7.39 (1H, d), 4.99 (2H, s), 3.86 (3H, s), 2.35 (3H, s)

b) 5-Cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid.

The title compound was prepared from the product from step a) by the method of example 55, step c).

^{1}H NMR (DMSO-d6) δ 9.03 (1H, d), 8.19 (1H, d), 7.81 (1H, d), 7.68 - 7.56 (5H, m), 5.26 (2H, s), 2.27 (3H, s)
MS: APCI (-ve): 374 [M-1]

Example 67

3-(8-Chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) Methyl 3-(8-chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetate

The sub-title compound was prepared from the product of example 55, step a) and 4,8-dichloroquinoline by the method of example 55, step b).

^{1}H NMR ($CDCl_3$) δ 9.14 (1H, d), 7.89 (1H, d), 7.62 (1H, d), 7.57 (1H, s), 7.52 - 7.46 (2H, m), 7.43 - 7.35 (2H, m), 4.98 (2H, s), 3.85 (3H, s), 2.32 (3H, s)

b) 5-Cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyll-1*H*-indole-1-acetic acid

The title compound was prepared from the product from step a) by the method of example 55, step c).

^{1}H NMR (DMSO-d6) δ 9.11 (1H, d), 8.01 (1H, d), 7.81 (1H, d), 7.66 - 7.52 (5H, m), 5.26 (2H, s), 2.26 (3H, s)
MS: APCI (-ve): 374 [M-1]

Example 68

5-Cyano-2-methyl-3-(2-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

a) Methyl 5-Cyano-2-methyl-3-(2-methyl-4-quinolinyl)-1*H*-indole-1-acetate

The sub-title compound was prepared from the product of example 55, step a) and 4-chloro-2-methylquinoline by the method of example 55, step b).

^{1}H NMR ($CDCl_3$) δ 8.13 (1H, d), 7.74 - 7.69 (1H, m), 7.62 - 7.59 (2H, m), 7.49 (1H, dd), 7.44 - 7.39 (1H, m), 7.36 (1H, d), 7.29 (1H, s), 4.97 (2H, s), 3.84 (3H, s), 2.82 (3H, s), 2.32 (3H, s)

b) 5-Cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid.

The title compound was prepared from the product from step a) by the method of example 55, step c).

^{1}H NMR (DMSO-d6) δ 8.07 (1H, d), 7.82 - 7.79 (2H, m), 7.67 - 7.53 (5H, m), 5.26 (2H, s), 2.78 (3H, s), 2.26 (3H, s)
MS: APCI (-ve): 354 [M-1]

Example 69

3-(8-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

a) 8-chloro-4-(5-fluoro-2-methyl-1*H*-indol-3-yl)-quinoline

The sub-title compound was made by the method of example 31 step a) using 5-fluoro-2-methylindole and 4,8-dichloroquinoline.

b) 3-(8-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).

MS: APCI (-ve): 367 [M-1]

^{1}H NMR (DMSO-d6) δ9.06 (1H, d), 7.97 (1H, d), 7.73 (1H, d), 7.60 - 7.38 (3H, m), 6.95 (1H, m), 6.85 (1H, m), 4.66 (2H, s), 2.23 (3H, s)

Example 70

5-fluoro-2-methyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

a) 4-(5-fluoro-2-methyl-1*H*-indol-3-yl)-7-methyl-quinoline

The subtitle compound was made by the method of example 31 step a) using 5-fluoro-2-methylindole and 4-chloro-7-methylquinoline.

b) 5-fluoro-2-methyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).

MS: APCI (-ve):347 (M-1)

^{1}H NMR (DMSO-d6) δ 8.01 (1H, d), 7.76 - 7.61 (2H, m), 7.56 - 7.39 (2H, m), 7.37 (1H, s), 6.98 (1H, t), 6.85 (1H, m), 4.98 (2H, s), 2.71 (3H, s), 2.23 (3H, s)

Example 71

2-methyl-5-(trifluoromethyl)-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) 4-[2-methyl-5-(trifluoromethyl)-1*H*-indol-3-yl]-8-(trifluoromethyl)-quinoline

The subtitle compound was made by the method of example 31 step a) using 2-methyl-5-(trifluoromethyl)-indole and 4-chloro-8-(trifluoromethyl)- quinoline.

b) 2-methyl-5-(trifluoromethyl)-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).

MS: APCI (-ve): 451 (M-1)
^{1}H NMR (DMSO-d6) δ 9.13 (1H, d), 8.22 (1H, d), 7.97 (1H, d), 7.77 - 7.62 (3H, m), 7.46 (2H, d), 4.96 (2H, s), 2.29 (3H, s)

Example 72

3-(8-fluoro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid

a) 8-fluoro-4-[2-methyl-5-(trifluoromethyl)-1*H*-indol-3-yl]-quinoline

The sub-title compound was made by the method of example 31 step a) using 2-methyl-5-(trifluoromethyl)-indole and 4-chloro-8-fluoro-quinoline.

b) 3-(8-fluoro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).
MS: APCI (-ve): 401 [M-1]
^{1}H NMR (DMSO-d6) δ 9.03 (1H, d), 7.74 - 7.38 (7H, m), 4.85 (2H, s), 2.28 (3H, s)

Example 73

3-(8-chloro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid

a) 8-chloro-4-[2-methyl-5-(trifluoromethyl)-1*H*-indol-3-yl]-quinoline

The subtitle compound was made by the method of example 31 step a) using 2-methyl-5-(trifluoromethyl)-indole and 4,8-dichloroquinoline.

b) 3-(8-chloro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).
MS: APCI (-ve): 417 [M-1]
^{1}H NMR (DMSO-d6) δ 9.10 (1H, d), 7.98 (1H, d), 7.74 - 7.58 (3H, m), 7.56 - 7.38 (3H, m), 4.83 (2H, s), 2.29 (3H, s)

Example 74

3-(8-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)-1*H*-indole-1-acetic acid

a) 2-methyl-5-(methylsulfonyl)- 1*H*-indole

2-methyl-5-(methylsulfonyl)-3-(methylthio)- 1*H*-indole was prepared from 4-(methylsulfonyl)- aniline by the method of example 48, part a) and used to prepare the subtitle compound by the method of example 48, part b).

^{1}H NMR (DMSO-d6) δ11.50 (1H, s), 8.00 (1H, d), 7.63 - 7.35 (2H, m), 6.37 (1H, s), 3.13 (3H, s), 2.44 (3H, s)

b) 8-chloro-4-[2-methyl-5-(methylsulfonyl)-1*H*-indol-3-yl]- quinoline

The sub-title compound was made by the method of example 31 step a) using the product from step a) and 4,8-dichloroquinoline.

c) 3-(8-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step b).

MS: APCI (-ve): 427 [M-1]

^{1}H NMR (DMSO-d6) δ 9.12 (1H, d), 8.00 (1H, d), 7.78 - 7.60 (5H, m), 7.54 (1H, d), 4.89 (2H, s), 3.12 (3H, s), 2.29 (3H, s)

Example 75

2-methyl-3-(8-methyl-4-quinolinyl)-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid

a) 8-methyl-4-[2-methyl-5-(methylsulfonyl)-1*H*-indol-3-yl]- quinoline

The sub-title compound was made by the method of example 31 step a) using 2-methyl-5-(methylsulfonyl)- 1*H*-indole and 4-chloro-8-methylquinoline.

b) 2-methyl-3-(8-methyl-4-quinolinyl)-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).

MS: APCI (-ve): 407 [M-1]

^{1}H NMR (DMSO-d6) δ 9.03 (1H, d), 7.81 - 7.60 (4H, m), 7.55 - 7.35 (3H, m), 5.00 (2H, s), 3.10 (3H, s), 2.83 (3H, s), 2.29 (3H, s)

Example 76

2-methyl-5-(methylsulfonyl)-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid

a) 4-[2-methyl-5-(methylsulfonyl)-1*H*-indol-3-yl]-8-(trifluoromethyl)-quinoline

The sub-title compound was made by the method of example 31 step a) using 2-methyl-5-(methylsulfonyl)- 1*H*-indole and 4-chloro-8-(trifluoromethyl)- quinoline.

b) 2-methyl-5-(methylsulfonyl)-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid

The title compound was made by the method of example 31 step b) using the product from step a).
MS: APCI (-ve): 461 (M-1)
^{1}H NMR (DMSO-d6) δ 10.04 (1H, d), 9.13 (1H, d), 8.91 (1H, d), 8.62 - 8.51 (5H, m), 5.57 (2H, s), 4.01 (3H, s), 3.19 (3H, s)

Example 77
3-(7-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid
a) 7-chloro-4-[2-methyl-5-(methylsulfonyl)-1*H*-indol-3-yl]- quinoline
The sub-title compound was made by the method of example 31 step a) using 2-methyl-5-(methylsulfonyl)-1*H*-indole and 4,7-dichloroquinoline.

b) 3-(7-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid
The title compound was made by the method of example 31 step b) using the product from step a).
MS: APCI (-ve): 427(M-1)
^{1}H NMR (DMSO-d6) δ 9.04 (1H, d), 8.19 (1H, d), 7.80 - 7.56 (6H, m), 5.04 (2H, s), 3.12 (3H, s), 2.29 (3H, s)

Example 78

5-chloro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) 4-(5-chloro-2-methyl-1*H*-indol-3-yl)-8-(methylsulfonyl)-quinoline

The sub-title compound was prepared by the method of Example 40 step a, using 5-chloro-2-methyl-1*H*-indole and 8-methanesulphonyl-4-chloroquinoline.

MS: APCI (+ve): 371 [M+H]

b) 5-chloro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 40 step b, using the product of step a.

MS: ESI (+ve): 457 $[M+H]^+$

c) 5-chloro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The sub-title compound was prepared by the method of Example 40 step c, using the product of step b.

MS: ESI (-ve): 427 [M-H]

^{1}H NMR (DMSO-d6) δ 9.15-7.42 (6H, M), 7.12 - 7.09 (2H, m), 4.54-4.45 (2H, m), 3.67 (3H, s), 2.23 (3H, s)

Example 79

5-Fluoro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

a) 4-(5-fhloro-2-methyl-1*H*-indol-3-yl)-8-(methylsulfonyl)-quinoline

The sub-title compound was prepared by the method of Example 40 step a, using 5-fluoro-2-methyl-1*H*-indole and 8-methanesulphonyl-4-chloroquinoline.

MS: APCI (+ve): 355 [M+H]

b) 5-fluoro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid, ethyl ester

The sub-title compound was prepared by the method of Example 40 step b, using the product of step a.

MS: ESI (+ve): 441 $[M+H]^+$

c) 5-fluoro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid

The sub-title compound was prepared by the method of Example 40 step c, using the product of step b.

MS: ESI (-ve): 411 $[M+H]^-$

^1H NMR (DMSO-d6) δ 9.13-7.39 (6H, M), 6.97-6.86 (2H, m), 4.53-4.44 (2H, m), 3.67 (3H, s), 2.24 (3H, s).

REFERENCES

1) Gassmann , Berge, T.J., Gilbert, D.P., Berkeley, W.C., *JACS*, 96, 5495-5508, (1974).

Pharmacological Data

Ligand Binding Assay

[^{3}H]PGD_2 was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEKcells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100µg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25µg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

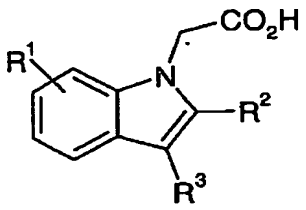
Each assay contained 20µl of 6.25nM [^{3}H]PGD_2, 20µl membrane saturated SPA beads both in assay buffer and 10µl of compound solution or 13,14-dihydro-15-keto prostaglandin D_2 ($DK\text{-}PGD_2$, for determination of non-specific binding, Cayman chemical

company). Compounds and DK-PGD_2 were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at room temperature for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC_{50} value of less than (<) 10μM.
Specifically, example 14 has a $pIC_{50} = 7.7$, example 36 has a $pIC_{50} = 8.15$ and example 55 has a $pIC_{50} = 7.27$.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which

in which
R^1 is hydrogen, halogen, CN, nitro, SO_2R^4, OH, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, heteroaryl, aryl (optionally substituted by chlorine or fluorine), C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0,1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, CH_2OH, CH_2OR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0, 1 or 2;

R^3 is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, OH, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9CO_2H, NR^9COR^4, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{1-6} alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x = 0,1 or 2;
with the proviso that R^3 cannot be phenyl or substituted phenyl;

R^4 represents aryl, heteroaryl, or C_{1-6}alkyl all of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10}

and $NR^{11}R^{12}$, $S(O)_xR^{13}$ (where x = 0,1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^8 and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$, $SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x = 0,1 or 2, NR^{16}, and itself optionally substituted by C_{1-3} alkyl;

R^7 and R^{13} independently represent a C_1-C_6, alkyl, an aryl or a heteroaryl group all of which maybe optionally substituted by one or more halogen atoms;

R^8 represents a hydrogen atom, $C(O)R^9$, C_1-C_6 alkyl an aryl or a heteroaryl group, all of which may be optionally substituted by halogen atoms or an aryl group;

each of R^9 R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6 alkyl, an aryl or a heteroaryl group, all of which may be optionally substituted by a halogen atom; and

R^{16} is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, $COYC_1$-C_4alkyl where Y is O or NR^7.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear branched, or cyclic.

2. A compound according to claim 1 in which R^1 is hydrogen or C_{1-6}alkyl optionally substituted by halogen, C_{1-6}alkoxy, alkylsulfone, cyano, $NR^9SO_2R^4$ or NR^9COR^4.

3. A compound according to claim 1 or 2 in which R^2 is hydrogen, C_{1-6}alkyl or C_{1-6}alkyl optionally substituted by OR^8.

4. A compound according to claim 3 in which R^3 is a 6,6 or 6,5-fused bicyclic aromatic ring containing at least one heteroatom and optionally substituted as defined in claim 1.

5. A compound according to claim 3 in which R^3 is quinoline, 1,2-benzisothiazole, benzo[b]thiophene or indole each of which is optionally substituted as defined in claim 1.

6. A compound according to claim 3 in which R^3 is quinoline is attached to the indole at the 4 position.

7. A compound according to any one of claims 4 to 6 in which the substituent(s) on R^3 is (are) hydrogen, methyl, trifluoromethyl, methoxy, fluoro, chloro, methylsulfone or cyano.

8. A compound according to claim 1 selected from:
3-(2-chloro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid;
2-methyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-5-methoxy-2-methyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2,6-dimethyl-1*H*-indole-1-acetic acid;
3-(2-chloro-4-quinolinyl)-2,4-dimethyl-1*H*-indole-1-acetic acid;
3-(2-benzothiazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(6-fluoro-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(1-isoquinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(6-methoxy-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(4-quinolinyl)-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(2-benzoxazolyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid,3-(7-chloro-4-quinolinyl)-2,5-dimethyl-6-(methylsulfonyl)-1*H*-indole-1-acetic acid;
3-(8-fluoro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(2,8-dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
2,5-dimethyl-3-[7-(trifluoromethyl)-4-quinolinyl]-1H-indole-1-acetic acid;
3-(8-bromo-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(8-methoxy-2-methyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(6,8-dimethyl-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2,5-dimethyl-1H-indole-1-acetic acid;

3-(7-chloro-4-quinolinyl)-2-methyl-5-nitro-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(6-methoxy-2-methyl-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
5-methoxy-2-methyl-3-(8-methyl-4-quinolinyl)-1H-indole-1-acetic acid, sodium salt;
3-(7-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]- 1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-(8-methyl-4-quinolinyl)- 1*H*-indole-1-acetic acid;
2-methyl-3-(8-methyl-4-quinolinyl)-5-(trifluoromethyl)- 1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-chloro-2-methyl-1*H*-indol-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-4-methyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-2,4-dimethyl-1*H*-indole-1-acetic acid;
3-(8-nitroquinolin-4-yl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-(8-cyano-4-quinolinyl)-2,5-dimethyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-(1,5-naphthyridin-4-yl)-1*H*-indole-1-acetic acid;
3-[8-(difluoromethoxy)-4-quinolinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;
5-amino-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2-methyl-5-[(methylsulfonyl)amino]-1*H*-indole-1-acetic acid;
5-(acetylamino)-3-(7-chloro-4-quinolinyl)-2-methyl-1*H*-indole-1-acetic acid;
3-(1,2-benzisothiazol-3-yl)-7-chloro-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
3-(1,2-benzisothiazol-3-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
3-(7-chloro-4-quinolin-4-yl)-5-fluoro-2,4-dimethyl-1*H*-indol-1-yl]acetic acid;
5-chloro-2-methyl-3-(8-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-[3,5'-bi-1*H*-indole]-1-acetic acid;
3-benzo[*b*]thien-3-yl-5-chloro-2-methyl-1*H*-indole-1-acetic acid;
2,5-dimethyl-3-thieno[2,3-*d*]pyrimidin-4-yl 1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-(hydroxymethyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-(methoxymethyl)-1*H*-indole-1-acetic acid;
2-[(acetyloxy)methyl]-5-chloro-3-(7-chloro-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylamino)methyl]-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-5,8-dihydro-4-quinolinyl)-2-(1-pyrrolidinylmethyl)-1*H*-indole-1-acetic acid;
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylthio)methyl]-1*H*-indole-1-acetic acid;

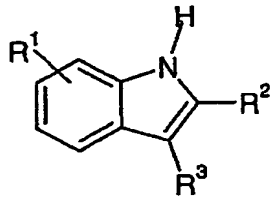
5-chloro-3-(7-chloro-4-quinolinyl)-2-[(methylsulfonyl)methyl]-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-4-methoxy-2-methyl-1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-(8-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-5-cyano-2-methyl-1*H*-indole-1-acetic acid;
5-cyano-2-methyl-3-(2-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-5-fluoro-2-methyl-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-(7-methyl-4-quinolinyl)-1*H*-indole-1-acetic acid;
2-methyl-5-(trifluoromethyl)-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(8-fluoro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2-methyl-5-(trifluoromethyl)-1*H*-indole-1-acetic acid;
3-(8-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)-1*H*-indole-1-acetic acid;
2-methyl-3-(8-methyl-4-quinolinyl)-5-(methylsulfonyl)-1*H*-indole-1-acetic acid;
2-methyl-5-(methylsulfonyl)-3-[8-(trifluoromethyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
3-(7-chloro-4-quinolinyl)-2-methyl-5-(methylsulfonyl)- 1*H*-indole-1-acetic acid;
5-chloro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
5-fluoro-2-methyl-3-[8-(methylsulfonyl)-4-quinolinyl]-1*H*-indole-1-acetic acid;
and pharmaceutically acceptable salts thereof.

9. A compound of formula (I) according to any one of claims 1 to 8 for use in therapy.

10. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 8.

11. A method according to claim 10 wherein the disease is asthma or rhinitis.

12. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

$L\text{-}CH_2CO_2R^{17}$ (III)

where R^{17} is an ester forming group and L is a leaving group in the presence of a base, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R^{17} to the corresponding acid
- forming a pharmaceutically acceptable salt.

13. A compound of formula (II) as defined in claim 9.

INTERNATIONAL SEARCH REPORT

PCT/SE 03/00855

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, 417/04, 413/04, 495/04, 471/04, A61K 31/4709, 31/428, 31/423, 31/405, 31/519, 31/4725, A61P 11/06, 11/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, CHEM.ABS.DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0147922 A2 (AVENTIS PHARMA LIMITED), 5 July 2001 (05.07.01), claims 23-29, 55-59, page 252, line 16 - page 259, line 27, RN 348638-09-5 --	1-13
X	WO 0078761 A1 (SEPRACOR, INC.), 28 December 2000 (28.12.00), figure 10, the claims, page 6, line 20 - page 7, line 24 --	1-13
X	STN International, File CAPLUS, CAPLUS accession no. 2001:235566, document no. 134:266203, Kato, Susumu et al: "Preparation and application of benzopyranone derivatives"; & JP,A2,2001089471, 20010403, RN 332082-10-7 --	1-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2003	25 -08- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00855

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1980:6356, Document no. 92:6356, Gabrielyan, G. E. et al: "Indole derivatives. LX. Synthesis of indole compounds with a furan ring", & Armyanskii Khimicheskii Zhurnal (1979), 32(4), 309-14, RN 51842-57-0	13
X	Tetrahedron Letters, Volume 42, No 31, 2001, Ulrike Hary et al: "Efficient synthesis of 3-(4,5-dihydro-1H-imidazole-2-yl)-1H-indoles", pages 5187-5189	13
X	EP 0924209 A1 (ELI LILLY AND COMPANY), 23 June 1999 (23.06.99), page 58; page 88	13
A	WO 9909007 A1 (AMERICAN HOME PRODUCTS CORPORATION), 25 February 1999 (25.02.99)	1-13
A	WO 9813368 A1 (ASTRA AKTIEBOLAG), 2 April 1998 (02.04.98), the claims, page 7, line 14 - line 18	1-13
A	EP 1170594 A2 (PFIZER LIMITED), 9 January 2002 (09.01.02), page 22, line 6 - line 21; page 34, figure 10 B (c)	1-13
A	GB 1356834 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED), 19 June 1974 (19.06.74)	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.
PCT/SE 03/00855

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INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.
PCT/SE 03/00855

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		AT 328433 B	25/03/76

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00855

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10,11
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 10-11 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.